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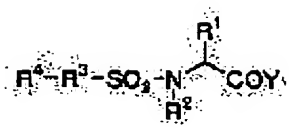
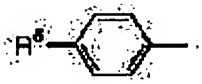
TSUZUKI HIROSHIGE

(54) **MMP-8 INHIBITOR**

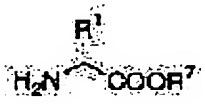


I

II



III



IV

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain an inhibitor of MMP-8, which is a kind of matrix meta- protease(MMP), of and useful as a medicament capable of inhibiting the crisis and progression of morbid states accompanied with histotripsy such as chronic rheumatoid arthritis, arthrosis deformans, etc., by using a novel sulfonamide derivative.
SOLUTION: This MMP-8 inhibitor contains a compound expressed by formula I {R1 is a (substituted) lower alkyl or a (substituted) aryl; R2 is H, a lower alkyl or an aralkyl; R3 is a group of formula III or a single bond; R4 is a group expressed by formula III [R5 is H, a (substmtuted) lower alkyl or the like], 2-halophenyl or the like; Y is NHOH or OH}, its optically active substance, their pharmaceutically allowable salts or their hydrate. The compound of the formula I is obtained, e.g. by reacting a compound expressed by R4-R3-SO2-Hal with an α-amino acid of formula IV (R7 is H or a carboxy-protected group).

LEGAL STATUS

[Date of request for examination]

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[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

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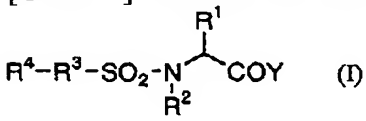
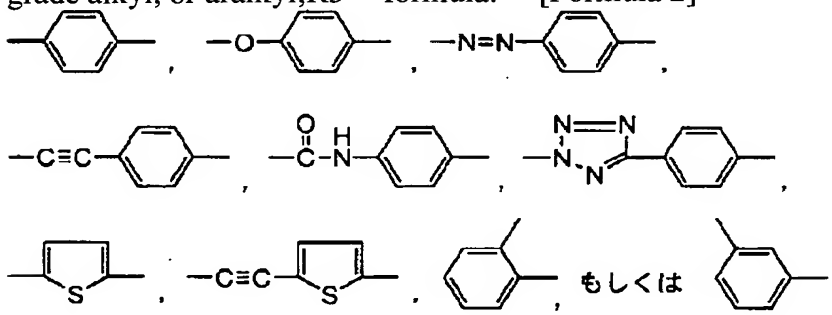
CLAIMS

[Claim(s)]
[Claim 1] General formula (I): [Formula 1]

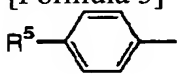


(I)

the low-grade alkyl by which R1 may be permuted among [type, the aryl which may be permuted, the aralkyl which may be permuted, the heteroaryl which may be permuted, or heteroarylalkyl;R2 which may be permuted -- a hydrogen atom, low-grade alkyl, or aralkyl;R3 -- formula: -- [Formula 2]

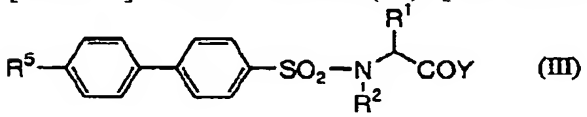


the radical come out of and expressed, or single bond;R4 -- general formula (II): -- [Formula 3]



(II)

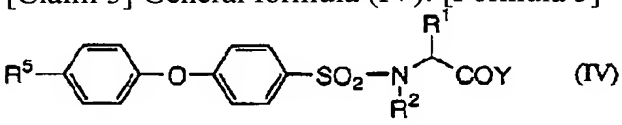
the low-grade alkyl by which R5 is permuted by the hydrogen atom, low-grade alkyl, the halogen, or HIDOROKISHI among the formula -- A halogen, the amino which may be permuted, low-grade alkyloxy, low-grade alkylthio, A phenyl, low-grade alkylcarbonyloxy, and amino sulfonyl or the radical expressed with hydroxy one, 2-halophenyl, 2-thienyl, 3-dibenzofuranyl [by which the 8th place was permuted by nitroglycerine or amino], phenyl ethenyl, or low-grade alkyl;Y is NHOH or OH (however, R3 is single bond when R4 is low-grade alkyl).] MMP-8 inhibitor which comes out and contains the compound shown, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.
[Claim 2] General formula (III): [Formula 4]



(III)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

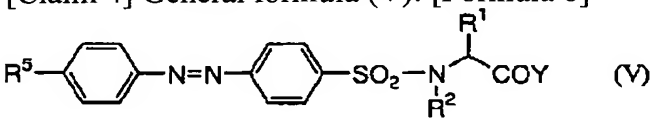
[Claim 3] General formula (IV): [Formula 5]



(IV)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

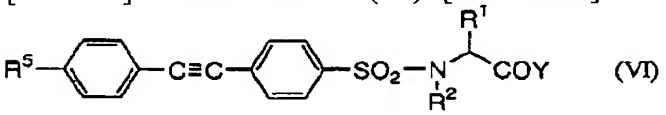
[Claim 4] General formula (V): [Formula 6]



(V)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

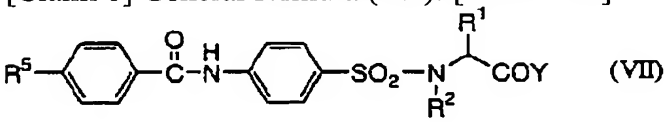
[Claim 5] General formula (VI): [Formula 7]



(VI)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

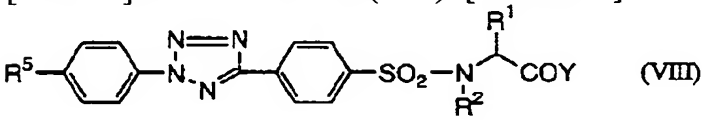
[Claim 6] General formula (VII): [Formula 8]



(VII)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

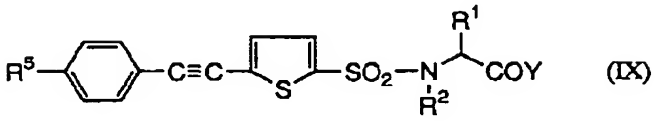
[Claim 7] General formula (VIII): [Formula 9]



(VIII)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

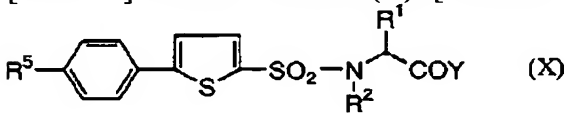
[Claim 8] General formula (IX): [Formula 10]



(IX)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

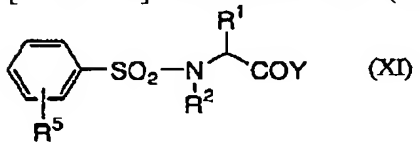
[Claim 9] General formula (X): [Formula 11]



(X)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

[Claim 10] General formula (XI): [Formula 12]



(XI)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

[Claim 11] MMP-8 inhibitor according to claim 1 to 10 which is the low-grade alkyl by which R1 may be permuted, the aralkyl which may be permuted, or heteroarylalkyl which may be permuted.

[Claim 12] MMP-8 inhibitor according to claim 1 to 11 whose R2 is a hydrogen atom, methyl, or benzyl.

[Claim 13] MMP-8 inhibitor according to claim 1 to 12 whose asymmetrical carbon which adjoins R1 is R arrangement.

[Claim 14] MMP-8 inhibitor according to claim 1 to 13 which is the remedy of rheumatoid arthritis.

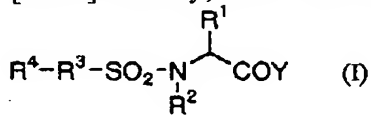
[Claim 15] MMP-8 inhibitor according to claim 1 to 13 which is the remedy of the osteoarthritis.

[Translation done.]

DETAILED DESCRIPTION

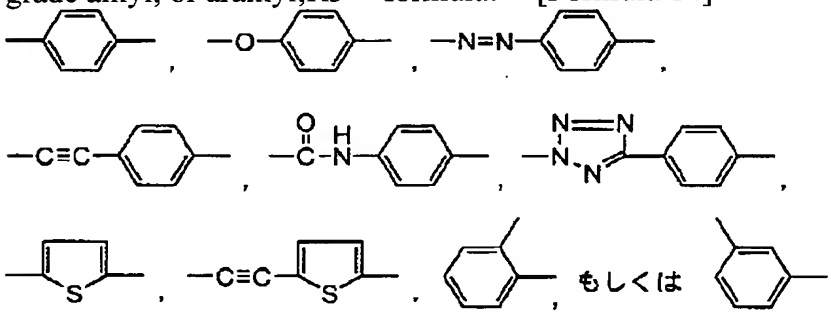
[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the inhibitor of MMP-8 which is a kind of a matrix METARO protease (MMP).
[0002]
[Description of the Prior Art] An extra-cellular matrix consists of a collagen, fibronectin, a laminin, proteoglycan, etc., and has roles, such as an organization support function, growth of a cell, differentiation, and adhesion. The METARO protease which is a protease containing a metal ion, especially the matrix METARO protease (MMP) are participating in the active center at decomposition of an extra-cellular matrix. Many families are reported to MMP from MMP-1 (I-beam collagenase) to MMP-18, and it is acting on growth, organization reform, etc. under original physiology conditions. However, it is reported by the various symptoms (transition of hypertrophic arthritis, articular rheumatism, a corneal ulcer, gum disease, and a neoplasm or seepage, viral infectious disease (HIV infectious disease)) accompanied by organization destruction or fibrosis that progress of symptoms and manifestation (activity) lifting of said enzyme correlate. For example, the intervention of MMP-8 (neutrophil leucocyte collagenase) is suggested to inflammation like MMP-1 (I-beam collagenase) and MMP-3 (SUTOROME lysin). If neutrophil leucocyte (polymorphonuclear leukocyte) permeates in an inflammatory response, MMP-8 will be emitted and it will mainly be concerned with decomposition of I, II, and an III mold collagen. Now, although the relation about MMP-8 and symptoms is not clear, MMP-8 are just going to be in agreement in that it is concerned with the symptoms accompanied by organization destruction. Therefore, MMP-8 inhibitor controls cartilage destruction of a joint and is expected as remedies, such as rheumatoid arthritis and osteoarthritis. The compound which has MMP-8 inhibitory action in this invention is indicated by WO 97/27174. Moreover, as related application, WO 95/35276, EP0757037-A2, JP,9-104672,A, and WO 97/45402 are mentioned. As MMP-8 inhibitor, beta-carboline derivative (WO 97/37658) and the dipeptide derivative (WO 96/013175) are known.
[0003]
[Problem(s) to be Solved by the Invention] in view of the above, this invention persons have inquired by it being alike and being attached to MMP-8 inhibitor as drugs which control the onset of the symptoms accompanied by organization destruction of rheumatoid arthritis, the osteoarthritis, etc., and progress.
[0004]
[Means for Solving the Problem] this invention persons are FEBS. MMP-8 inhibition activity was measured using the approach of LETT., 296 and 1992, and 263 -366 publication, and the invention of a compound which has MMP-8 strong inhibitory action was tried. Consequently, a certain kind of sulfonamide derivative found out

having MMP-8 strong inhibitory action.
[0005] namely, this invention -- I general formula (I): -- [Formula 13]

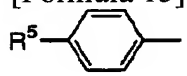


(I)

the low-grade alkyl by which R1 may be permuted among [type, the aryl which may be permuted, the aralkyl which may be permuted, the heteroaryl which may be permuted, or heteroarylalkyl;R2 which may be permuted -- a hydrogen atom, low-grade alkyl, or aralkyl;R3 -- formula: -- [Formula 14]

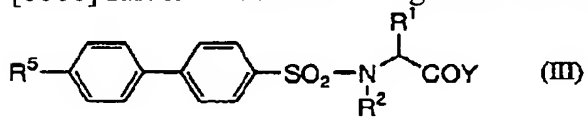


the radical come out of and expressed, or single bond;R4 -- general formula (II): -- [Formula 15]



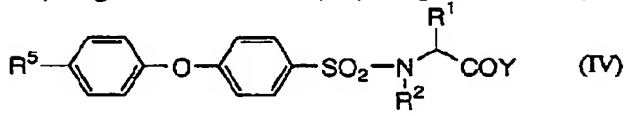
(II)

the low-grade alkyl by which R5 is permuted by the hydrogen atom, low-grade alkyl, the halogen, or HIDOROKISHI among the formula -- A halogen, the amino which may be permuted, low-grade alkyloxy, low-grade alkylthio, A phenyl, low-grade alkylcarbonyloxy, and amino sulfonyl or the radical expressed with hydroxy one, 2-halophenyl, 2-thienyl, 3-dibenzofuranyl [by which the 8th place was permuted by nitroglycerine or amino], phenyl ethenyl, or low-grade alkyl;Y is NHOH or OH (however, R3 is single bond when R4 is low-grade alkyl).] It is related with MMP-8 inhibitor which comes out and contains the compound shown, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.
[0006] further -- detailed -- II general formula (III): -- [Formula 16]



(III)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.
III) -- general formula (IV): -- [Formula 17]

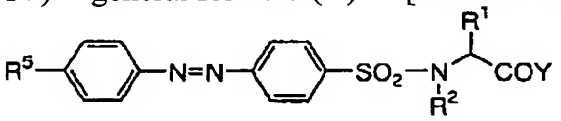


(IV)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are

shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

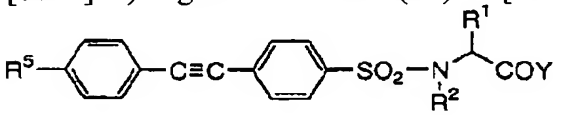
IV) -- general formula (V): -- [Formula 18]



(V)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

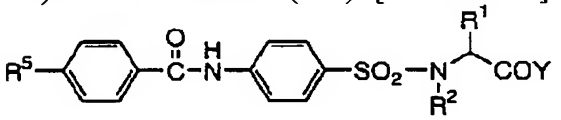
[0007] V) -- general formula (VI): -- [Formula 19]



(VI)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

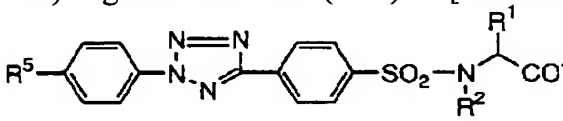
VI) General formula (VII): [Formula 20]



(VII)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

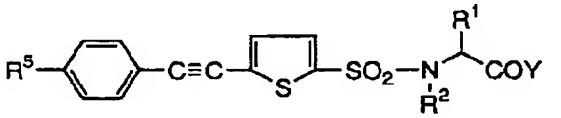
VII) -- general formula (VIII): -- [Formula 21]



(VIII)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

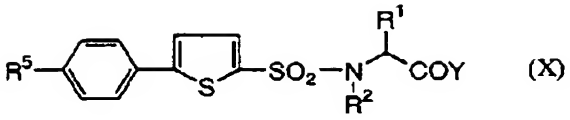
[0008] VIII) -- general formula (IX): -- [Formula 22]



(IX)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

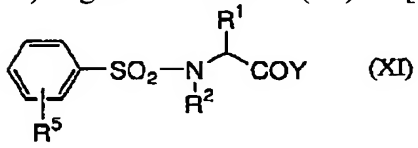
IX) -- general formula (X): -- [Formula 23]



(X)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

X) -- general formula (XI): -- [Formula 24]



(XI)

(-- MMP-8 inhibitor which contains the compound in which R1, R2, R5, and Y are shown by the above and this meaning) among a formula, its optically active substance, the salts which are permitted on those medicine manufacture, or those hydrates as an active principle.

XI) MMP-8 inhibitor given in either of I-X which are the low-grade alkyl by which R1 may be permuted, the aralkyl which may be permuted, or heteroarylalkyl which may be permuted.

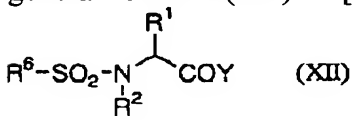
XII) MMP-8 inhibitor given in either of I-XI(s) whose R2 is a hydrogen atom, methyl, or benzyl.

[0009] XIII) MMP-8 inhibitor given in either of the claims I-XII whose asymmetrical carbon which adjoins R1 is R arrangement.

XIV) MMP-8 inhibitor given in either I which is the remedy of rheumatoid arthritis - XIII.

XV) It is related with MMP-8 inhibitor given in either I which is the remedy of the osteoarthritis - XIII.

[0010] although all the above-mentioned compounds have MMP-8 inhibitory action -- general formula (XII): -- [Formula 25]

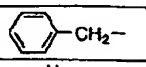
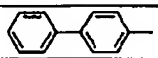
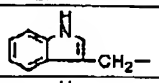
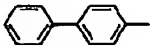
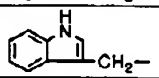
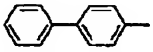
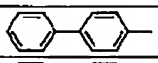
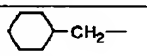
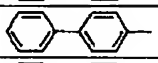
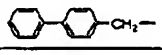
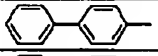
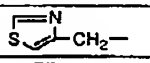
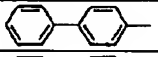
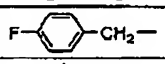
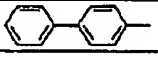
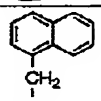
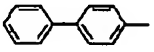
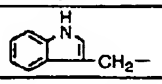
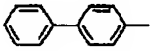
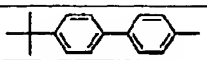
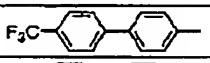
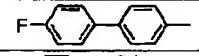
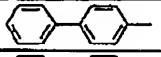
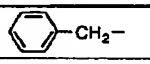
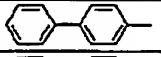
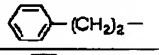
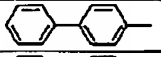
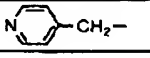
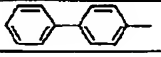


(XII)

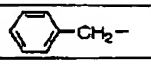
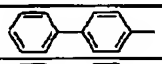
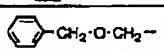
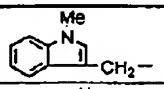
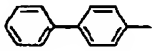
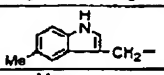
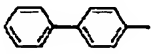
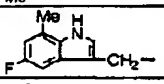
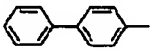
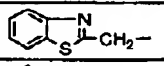
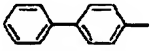
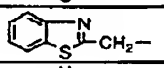
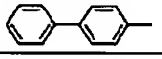
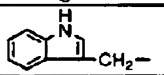
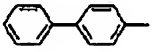
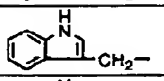
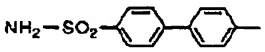
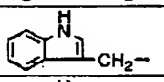
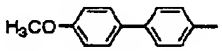
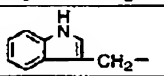
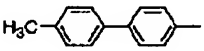
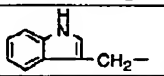
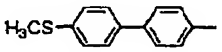
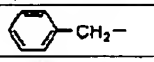
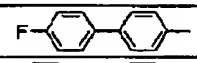
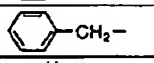
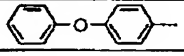
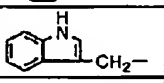
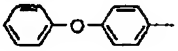
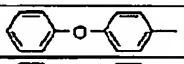
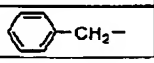
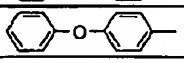
Especially the compound that is alike, sets and is expressed below is desirable.

[0011]

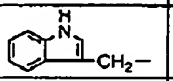
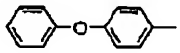
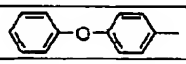
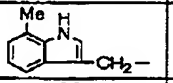
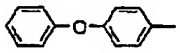
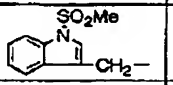
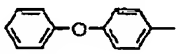
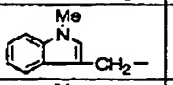
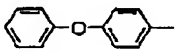
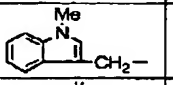
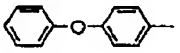
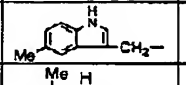
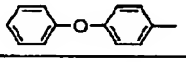
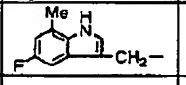
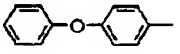
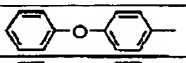
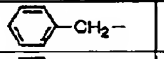
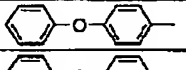
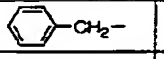
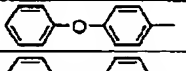
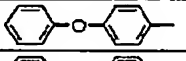
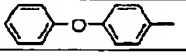
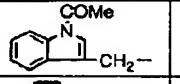
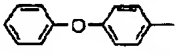
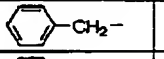
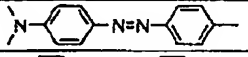
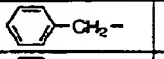
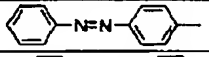
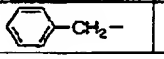
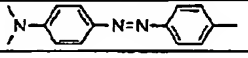
[Formula 26]

化合物 No.	Y	R^1	R^2	R^3
1	OH		H	
2	OH		H	
3	NHOH		H	
4	NHOH	CF_3CH_2-	H	
5	NHOH		H	
6	NHOH		H	
7	NHOH	HO_2HC-	H	
8	NHOH		H	
9	NHOH		H	
10	NHOH		H	
11	NHOH		CH_3	
12	OH	$(CH_3)_2CH$-	H	
13	OH	$(CH_3)_2CH$-	H	
14	OH	$(CH_3)_2CH$-	H	
15	OH	$HOOCCH_2CH_2$-	H	
16	NHOH		H	
17	NHOH		H	
18	NHOH		H	

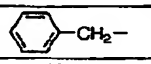
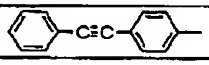
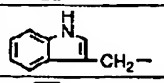
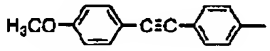
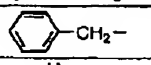
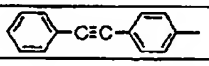
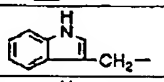
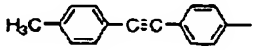
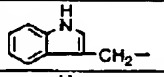
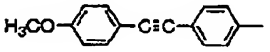
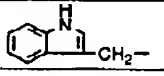
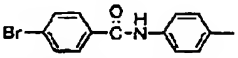
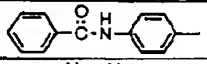
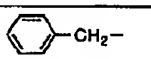
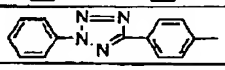
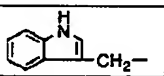
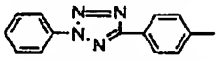
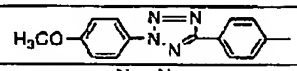
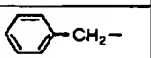
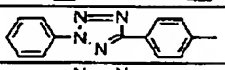
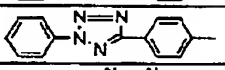
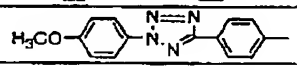
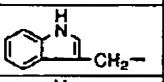
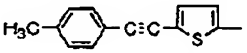
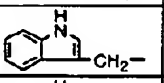
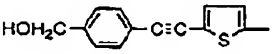
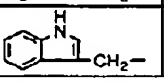
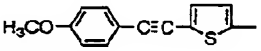
[0012]
[Formula 27]

化合物 No.	Y	R^1	R^2	R^6
19	NHOH		H	
20	NHOH		H	
21	NHOH		H	
22	NHOH		H	
23	NHOH		H	
24	OH		H	
25	NHOH		H	
26	NHOH		$PhCH_2$-	
27	OH		H	
28	OH		H	
29	OH		H	
30	OH		H	
31	OH		H	
32	OH		H	
33	OH		H	
34	OH	$(CH_3)_2CH$-	H	
35	NHOH		H	

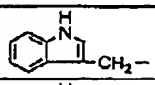
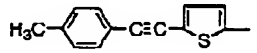
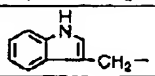
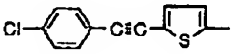
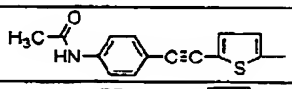
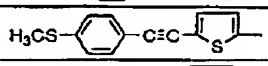
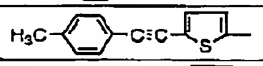
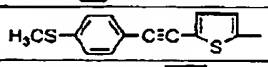
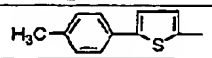
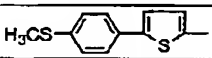
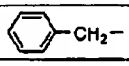
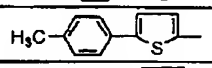
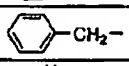
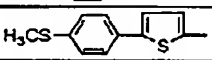
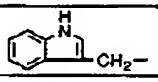
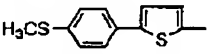
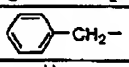
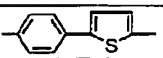
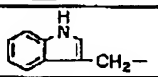
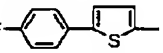
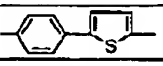
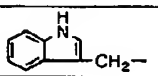
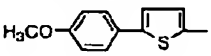
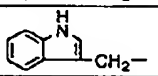
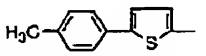
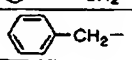
[0013]
[Formula 28]

化合物 No.	Y	R¹	R²	R⁶
36	NHOH		H	
37	NHOH	$(CH_3)_2CH$-	H	
38	OH		H	
39	OH		H	
40	OH		H	
41	NHOH		H	
42	NHOH		H	
43	NHOH		H	
44	OH	$(CH_3)_2CH$-	$PhCH_2$-	
45	NHOH		CH_3	
46	NHOH		$PhCH_2$-	
47	NHOH	$(CH_3)_2CH$-	CH_3	
48	NHOH	$(CH_3)_2CH$-	$PhCH_2$-	
49	NHOH		H	
50	OH		H	
51	NHOH		H	
52	NHOH		H	

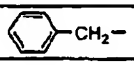
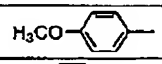
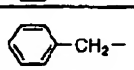
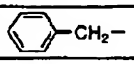
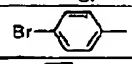
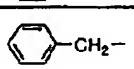
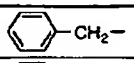
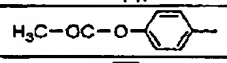
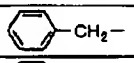
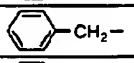
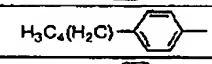
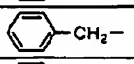
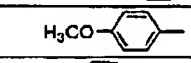
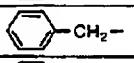
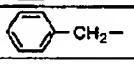
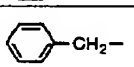
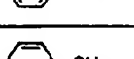
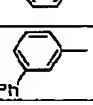
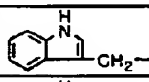
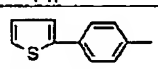
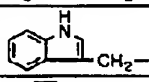
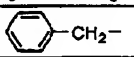
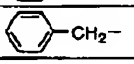
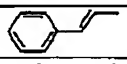
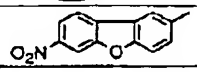
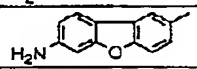
[0014]
[Formula 29]

化合物 No.	Y	R^1	R^2	R^6
53	OH		H	
54	OH		H	
55	NHOH		H	
56	NHOH		H	
57	NHOH		H	
58	OH		H	
59	NHOH	$(CH_3)_2CH$-	H	
60	OH		H	
61	OH		H	
62	OH	$(CH_3)_2CH$-	H	
63	NHOH		H	
64	NHOH	$(CH_3)_2CH$-	H	
65	NHOH	$(CH_3)_2CH$-	H	
66	OH		H	
67	OH		H	
68	OH		H	

[0015]
[Formula 30]

化合物 No.	Y	R^1	R^2	R^6
69	NHOH		H	
70	NHOH		H	
71	OH	$(CH_3)_2CH$-	H	
72	OH	$(CH_3)_2CH$-	H	
73	NHOH	$(CH_3)_2CH$-	H	
74	NHOH	$(CH_3)_2CH$-	H	
75	OH	$(CH_3)_2CH$-	H	
76	OH	$(CH_3)_2CH$-	H	
77	OH		H	
78	OH		H	
79	OH		H	
80	OH		H	
81	OH		H	
82	OH	$(CH_3)_2CH$-	H	
83	OH		H	
84	OH		H	
85	NHOH		H	

[0016]
[Formula 31]

化合物 No.	Y	R^1	R^2	R^6
86	NHOH		H	
87	NHOH		H	
88	NHOH		H	
89	NHOH		H	
90	NHOH		H	
91	NHOH		H	
92	NHOH		H	
93	NHOH		H	
94	NHOH		$PhCH_2$-	
95	NHOH		$PhCH_2$-	
96	NHOH		H	
97	NHOH		H	
98	OH		H	
99	NHOH		$PhCH_2$-	
100	NHOH		H	$CH_3(CH_2)_6CH_2$-
101	NHOH		H	
102	OH	$(CH_3)_2CH$-	H	
103	OH	$(CH_3)_2CH$-	H	

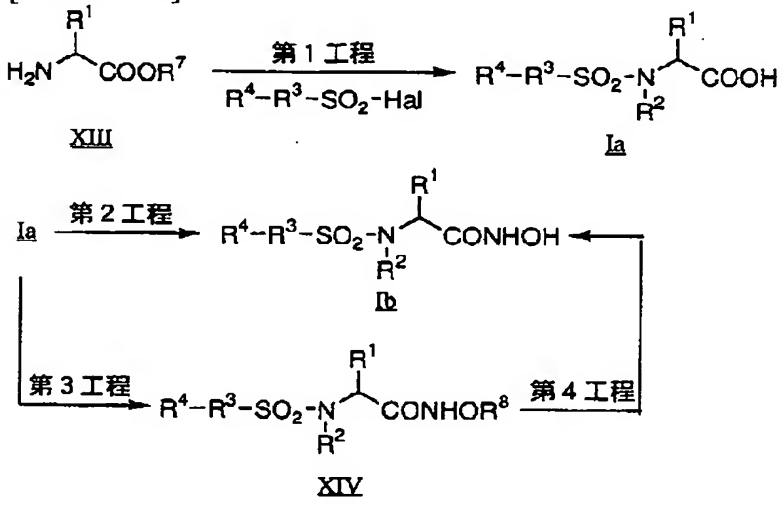
[0017] The compound expressed with 18 (compound No.), 28, 29, 30, 41, 57, 65, 68, 72, 78, 79, 83, and 84 is mentioned especially preferably. The compound expressed with 78 (compound No.), 79, and 84 is mentioned still more preferably. R1 Isopropyl, trifluoromethyl, hydroxymethyl, cyclohexyl methyl, Carboxyethyl, benzyloxymethyl, benzyl, phenylethyl, 4-fluoro benzyl, 4-phenyl benzyl, 1-naphthyl methyl, 4-pyridyl methyl, methyl (thiazole-4-IRU), methyl (benzothiazole-3-IRU), Methyl, methyl (1-methylindole-3-IRU), (Indore-3-IRU) Methyl, methyl (1-acetyl-Indore-3-IRU), (1-methylsulfonyl-Indore-3-IRU) (5-methylindole-3-IRU) Methyl, methyl (5-fluoro-Indore-3-IRU), and methyl (7-methylindole-3-IRU) are desirable. Moreover, in a general formula (XI), the compound which R5 permuted by the 4th place is desirable.

[0018] "Low-grade alkyl" means C1 - C8 alkyl of the shape of the shape of a straight chain, and branching among this description. For example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, etc. are mentioned. The "low-grade alkyl" in R2 has methyl, ethyl, n-propyl, and desirable isopropyl. The "low-grade alkyl" in R4 has n-hexyl, n-heptyl, and desirable n-octyl. The "low-grade alkyl" in R5 has methyl, ethyl, n-propyl, isopropyl, n-butyl,

isobutyl, sec-butyl, tert-butyl, and desirable n-pentyl. "Aryl" means the shape of a monocycle, and condensed-ring-like aromatic hydrocarbon among this description. For example, phenyl, 1-naphthyl, 2-naphthyl, anthryl, etc. are mentioned. An "aralkyl" is what the above "aryl" permuted above "low-grade alkyl" among this description, and these can be combined in all replaceable locations. For example, benzyl, phenylethyl, phenylpropyl (for example, 3-phenylpropyl), naphthyl methyl (for example, 1-naphthyl methyl), anthryl methyl (for example, 9-anthryl methyl), etc. are mentioned. Benzyl and phenylethyl are desirable especially. "Heteroaryl" means the ring of 5 which contains in endocyclic [one or more] the oxygen atom, sulfur atom, or nitrogen atom chosen as arbitration - 6 members among this description, and this may condense with a ring or other heterocycles, and can combine these in all replaceable locations. For example, pyrrolyl (for example, 1-pyrrolyl), indolyl (For example, 3-indolyl), carbazolyl (for example, 3-carbazolyl), Imidazolyl (for example, 4-imidazolyl), pyrazolyl (For example, 1-pyrazolyl), benzoimidazolyl (for example, 2-benzoimidazolyl), Indazolyl (for example, 3-indazolyl), in DORIJINIRU (For example, 6-in DORIJINIRU), pyridyl (for example, 4-pyridyl), Quinolyl (for example, 5-quinolyl), iso quinolyl (for example, 3-iso quinolyl), AKURIJIRU (for example, 1-AKURIJIRU), phenanthrolizinyl (For example, 2-phenanthrolizinyl), pilus DAJINIRU (for example, 3-pilus DAJINIRU), Pyrimidinyl (for example, 4-pyrimidinyl), pyrazinyl (For example, 2-pyrazinyl), SHINNORINIRU (for example, 3-SHINNORINIRU), Phthalazinyl (for example, 2-phthalazinyl), chinae-cortex ZORINIRU (For example, 2-chinae-cortex ZORINIRU), isoxazolyl (for example, 3-isoxazolyl), Benzoisoxazolyl (for example, 3-benzoisoxazolyl), oxazolyl (For example, 2-oxazolyl), benzoxazolyl (for example, 2-benzoxazolyl), Benzooxadiazolyl (for example, 4-benzooxadiazolyl), Iso thiazolyl (for example, 3-iso thiazolyl), BENZO iso thiazolyl (For example, 2-BENZO iso thiazolyl), thiazolyl (for example, 4-thiazolyl), Benzothiazolyl (for example, 2-benzothiazolyl), a furil (for example, 3-furil), a benzofuril (for example, 3-benzofuril), thienyl (for example, 2-thienyl), benzothienyl (for example, 2-benzothienyl), tetra-ZORIRU, etc. are mentioned.
[0019] "Heteroarylalkyl" is what the above "heteroaryl" permuted by the location of the arbitration of the above "low-grade alkyl" among this description, and these can be combined in all replaceable locations. For example, thiazolyl methyl (for example, 4-thiazolyl methyl), thiazolyl ethyl (For example, 5-thiazolyl-2-ethyl), benzothiazolyl methyl (For example, methyl (benzothiazole-2-IRU)), indolyl methyl (For example, methyl (Indore-3-IRU)), imidazolyl methyl (For example, 4-imidazolyl methyl), benzothiazolyl methyl (For example, 2-benzothiazolyl methyl), benzopyrazolyl methyl (For example, 1-benzopyrazolyl methyl), benzotriazoryl methyl (For example, 4-benzotriazoryl methyl), benzoquinolyl methyl (for example, 2-benzoquinolyl methyl), benzoimidazolyl methyl (for example, 2-benzoimidazolyl methyl), pyridyl methyl (for example, 4-pyridyl methyl), etc. are mentioned. Methyl, methyl (benzothiazole-2-IRU), 4-thiazolyl methyl, and 4-pyridyl methyl are especially (Indore-3-IRU) desirable. A "halogen" means a fluorine, chlorine, a bromine, and iodine among this description. "Low-grade alkyloxy" means the alkyloxy whose alkyl part is the above "low-grade alkyl" among this description. For example, methyloxy, ethyloxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy, etc. are mentioned. Preferably, methyloxy, ethyloxy, n-propyloxy, and isopropyloxy are mentioned. "Low-grade alkylthio" means the alkylthio whose alkyl part is the above "low-grade alkyl" among this description. For example, a methylthio, ethyl thio, etc. are mentioned. "Low-grade alkylcarbonyloxy" means the low-grade alkylcarbonyloxy whose alkyl part is the above "low-grade alkyl" among this

description. For example, methyl carbonyloxy, ethyl carbonyloxy, n-propyl carbonyloxy, etc. are mentioned. "Halophenyl" means the phenyl permuted above "a halogen" among this description. For example, 4-fluoro phenyl, 4-chlorophenyl, 4-BUROMO phenyl, etc. are mentioned.
[0020] the inside of this description, and "the amino which may be permuted" -- the above "low-grade alkyl", an "aralkyl", "heteroarylalkyl", or acyl (for example, acetyl) -- 1 -- or it permutes two or more -- having -- **** -- **** -- good amino or unsubstituted amino is meant. For example, amino, methylamino, dimethylamino, ethyl methylamino, benzylamino, acetylamino, etc. are mentioned. Especially amino, dimethylamino, and acetylamino are desirable. As a substituent in "the alkyl which may be permuted" in R1, among this description, hydroxy ** Alkyloxy (for example, methyloxy, ethyloxy), mercapto, alkylthio (for example, methylthio) and cycloalkyl (for example, cyclo propyl --) Cyclo butyl, cyclopentyl, cyclohexyl, a halogen For example, (a fluorine, chlorine, a bromine and iodine), carboxy, low-grade alkyloxy carbonyl For example, (methyloxy carbonyl and ethyloxy carbonyl), nitroglycerine, Cyano ** low-grade halo alkyl (for example, trifluoromethyl), the amino (for example, methylamino, dimethylamino, carbamoyl amino) which may be permuted, guanidino, benzyloxy one, etc. are mentioned. These can be permuted in all one or more possible locations. As "alkyl which may be permuted", methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, hydroxymethyl, cyclohexyl methyl, carboxyethyl, and benzyloxymethyl are desirable. The inside of this description, "the aryl which may be permuted", "the aralkyl which may be permuted", With the substituent on the ring in "the heteroaryl which may be permuted", and "the heteroarylalkyl which may be permuted" for example, hydroxy ** low-grade alkyloxy (for example, methyloxy --) Ethyloxy, mercapto, low-grade alkylthio (for example, methylthio), Cycloalkyl (for example, cyclo propyl, cyclo butyl, cyclopentyl), A halogen (for example, a fluorine, chlorine, a bromine, iodine), carboxy, low-grade alkyloxy carbonyl For example, (methyloxy carbonyl and ethyloxy carbonyl), nitroglycerine, Cyano ** low-grade halo alkyl (for example, trifluoromethyl), aryloxy (For example, phenyloxy), the amino which may be permuted For example, (methylamino, dimethylamino, diethylamino, benzilideneamino), guanidino and low-grade alkyl (for example, methyl, ethyl, and n-propyl --) Isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neo-pentyl, tert-pentyl, The low-grade alkenyl (for example, vinyl, propenyl), alkynyl For example, (ethynyl and phenyl ethynyl), low-grade alkanoyl For example, (the formyl, acetyl and a propionyl), an acyloxy (For example, acetyloxy), acylamino, a low-grade alkyl sulfonyl (For example, methylsulfonyl), phenyl, benzyl, azo (for example, phenylazo), the heteroaryl (for example, 3-pyridyl) that may be permuted, the ureido (for example, ureido, phenyl ureido) which may be permuted are mentioned. These can be permuted in all one or more possible locations. As "an aralkyl which may be permuted", benzyl, phenylethyl, 4-fluoro benzyl, 4-phenyl benzyl, and 1-naphthyl methyl are mentioned. As "heteroarylalkyl which may be permuted" 4-pyridyl methyl, methyl (thiazole-4-IRU), methyl (benzothiazole-3-IRU), Methyl, methyl (1-methylindole-3-IRU), (Indore-3-IRU) Methyl, methyl (1-acetyl-Indore-3-IRU), (1-methylsulfonyl-Indore-3-IRU) (5-methylindole-3-IRU) Methyl, methyl (5-fluoro-Indore-3-IRU), and methyl (7-methylindole-3-IRU) are mentioned.
[0021]
[Embodiment of the Invention] The compound (I) which is this invention MMP-8 inhibitor can use as a start raw material the alpha-amino acid shown by the general formula (XIII), and can manufacture it with five kinds of synthesis methods shown

below. This compound is compoundable if A law is generally used. Moreover, even if it uses B law - E law, it is compoundable with a structural feature. These synthesis methods are indicated by WO 97/27174.
A law: The synthesis method about a compound (I) at large.
B law: The synthesis method about the compound whose R3 is (-(tetrazole)-(phenyl)-) in a general formula (I).
The C method: The synthesis method about the compound whose R3 is (-C(triple bond) C-(phenyl, thiophene)-) in a general formula (I).
The D method: The synthesis method about the compound whose R3 is (-C(=O)-NH-(phenyl)-) in a general formula (I).
E law: The synthesis method about the compound whose R3 is (-(phenyl)-) in a general formula (I).
These approaches are explained in detail below.
[0022] (A law)
[Formula 32]



(Among a formula, in the above, this meaning, and R7, hydrogen or a carboxy protective group, and R8 show a hydroxy protective group, and Hal shows [R1, R2 R3, and R4] a halogen)
[0023] The reaction from a compound (XIII) to a compound (Ia) is a reaction (the 1st process) which sulfonyl-izes the amino group of a compound (XIII). If it requires, N-alkylation, etc. clearance of a carboxy protective group, etc. will be performed after a reaction. The reaction from a compound (Ia) to a compound (Ib) is a reaction (the 2nd process) which hydroxamic-acid-izes carboxy. Moreover, after making the hydroxylamine which has a hydroxy protective group, or its acid addition salt act on a compound (Ia) from a compound (Ia) to a compound (Ib) and obtaining a compound (XIV) (the 3rd process), a deprotection reaction (the 4th process) may be given. What is necessary is just to perform sulfonyl-izing and a hydroxamic acid-ized reaction according to a conventional method. For example, a sulfonyl-ized reagent, for example, the sulfonic-acid halogenide expressed with R4-R3-SO2Hal (R3 and R4 above and this meaning; Hal= halogen), is made to react to the amino acid shown by the formula (XIII) under existence of a base, and, subsequently a hydroxylamine is made to react to it. It will be as follows if each process is described in more detail.
[0024] (The 1st process) Some things of the amino acid shown by the formula (XIII) of a raw material compound or its acid addition salt (for example, a hydrochloride, a p-toluenesulfonic-acid salt, a trifluoroacetic acid salt) can come to hand as a

commercial item. Other things are compoundable according to the approach of a publication etc. to 22 experimental science lectures, the amino acid synthesis method of the 4th-edition (edited by Chemical Society of Japan) publication, J.Med.Chem.38, and 1689-1700 (1995) Gary M.Ksander et.al. Moreover, some things of a sulfonyl-ized reagent (for example, sulfonic-acid halogenide) are available as a commercial item, and other things can be compounded according to an approach given in 14 new experimental science lecture, 1787-page, and (1978) Synthesis 852-854 (1986) Tatsuo Hamada et.al. etc. As a protected carboxyl group, the carboxy which turned ester (for example, methyl ester, tert-butylester, benzyl ester) is mentioned, for example. Although desorption of these protective groups is carried out by hydrolyzing according to a protective group under existence of an acid (for example, a hydrochloric acid, trifluoroacetic acid) or bases (for example, sodium hydroxide etc.), or carrying out catalytic reduction (for example, under 10% palladium-carbon catalyst existence), in order to obtain a compound (Ib), it may perform hydroxamic acid-ization of the 2nd process with ester. When it is the amino acid whose R7 is hydrogen in a compound (XIII) as a solvent of a sulfonyl-ized reaction, dimethylformamide, a tetrahydrofuran, dioxane, dimethyl sulfoxide, an acetonitrile, water, or these mixed solvents are desirable, but when R7 is the ester object which is a protective group, in addition to this, the mixed solvent of the above-mentioned solvent and a water-insoluble nature solvent (for example, benzene, dichloromethane) is mentioned. Inorganic bases, such as organic bases, such as triethylamine and N-methyl morpholine, or a sodium hydroxide, a potassium hydroxide, and potassium carbonate, etc. can be used for the base used for a sulfonyl-ized reaction. Reaction temperature is usually ice-cooling - a room temperature. in addition -- the case where it is the radical to which R1, R2, R3, or R4 in a compound (Ia) have a substituent (for example, hydroxy ** mercapto, amino, guanidino) acting as a failure in sulfonyl-ization -- Protective Groups in Organic Synthesis and Theodora W Green (John Wiley & Sons) etc. -- what is necessary is to protect beforehand by the approach of a publication and just to remove the protective group in a desirable phase moreover, the case where R2 is not hydrogen -- further -- inside of solvents, such as dimethylformamide, tetrahydrofuran, and dioxane, and bottom of ice-cooling -, preferably, alkyl halide, halogenation aralkyls (for example, a methyl iodide, an ethyl iodide, etc.) (for example, benzyl chloride, benzyl bromide, etc.), etc. can be added at the bottom of ice-cooling - a room temperature, and 80 degree C of two target N-R can be obtained by stirring preferably for 10 to 20 hours for 3 to 30 hours.

[0025] (The 2nd process) Hydroxamic acid (Ib) is manufactured by making a hydroxylamine act on a compound (Ia) or its reactant derivative. A hydroxylamine usually uses the acid addition salt (for example, a hydrochloride, phosphate, a sulfate; available as a commercial item) for a reaction under existence of a base. As a base, inorganic bases, such as organic bases, such as triethylamine, N.N-dimethylaniline, and N-methyl morpholine, or a sodium hydroxide, a potassium hydroxide, and potassium carbonate, can be used. When using a compound (Ia) as a raw material of hydroxamic-acid-izing as it is, it reacts to the bottom of existence of a peptide condensation reagent (for example, mixture with dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, N, and N'-carbonyldiimidazole or those either and 1-hydroxy benzotriazol, N-hydroxysuccinic acid imide, etc.) etc. As a solvent, dimethylformamide, a tetrahydrofuran, dioxane, dimethyl sulfoxide, an acetonitrile, water, or these mixed solvents are used, -20 degrees C - 40 degrees C of reaction temperature are ice-cooling - a room temperature preferably, and reaction time is 1 hour - 16 hours. As a reactant derivative of a compound (Ia), an acid

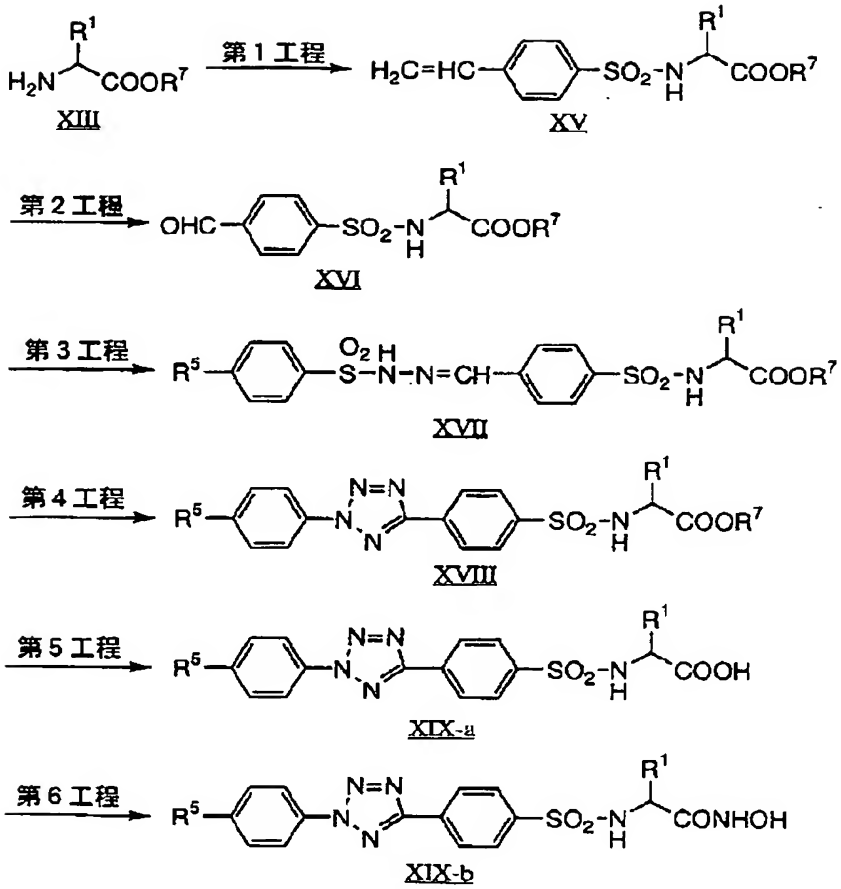
anhydride (especially mixed acid anhydride), acid halide, acid azide, or ester is used. Although these reactant derivatives are manufactured by the usual approach, an acid anhydride makes acid halide (for example, chloro ethyl carbonate) act on a compound (Ia) under existence of a base (for example, triethylamine), and acid halide makes a halogenation reagent (for example, oxalyl chloride, thionyl chloride) act on a compound (Ia), and can be manufactured. Moreover, although ester can be chosen from non-activity ester or activity ester Non-activity ester is set to a compound (XIII) at the 1st process. R7 A carboxy protective group That what is necessary is not to carry out deprotection of the product which sulfonyl-ized what is for example, (methyl, tert-butyl, and benzyl), but just to use it as it is activity ester -- a compound (Ia) -- a carbodiimide (for example, dicyclohexylcarbodiimide --) The hydroxy object corresponding to activity ester residue, such as a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, 1-hydroxy benzotriazol, or N-hydroxysuccinic acid imide, is made to act, and it can manufacture. The reaction condition of hydroxamic-acid-izing of the reactant derivative of a compound (Ia) is the same as that of hydroxamic-acid-izing when using a compound (Ia) as it is, and good. In addition, the reaction of the 1st process and the 2nd process may be performed by the single reaction tub (the so-called one pot).

[0026] (The 3rd process) As a protected hydroxylamine which is used at this process, O-benzyl hydroxylamine, O-(p-methoxybenzyl) hydroxylamine, O-(tert-butyl) hydroxylamine, etc. are mentioned, for example. A reaction condition is the same as the reaction condition in the 2nd process, and good.

(The 4th process) At this process, it leads to the compound which removes a protective group by processing with the catalytic reduction under a hydrogen ambient atmosphere, concentrated hydrochloric acid, or trifluoroacetic acid, and is shown by the target formula (Ib). Thus, isolation purification of the manufactured this invention compound (Ia) and the (Ib) can be carried out with well-known separation and purification means (for example, a chromatography, the crystallizing method, etc.).

[0027] (B law)

[Formula 33]



(The inside of a formula, and R1, R2, R5 and R7 are the above and this meaning)

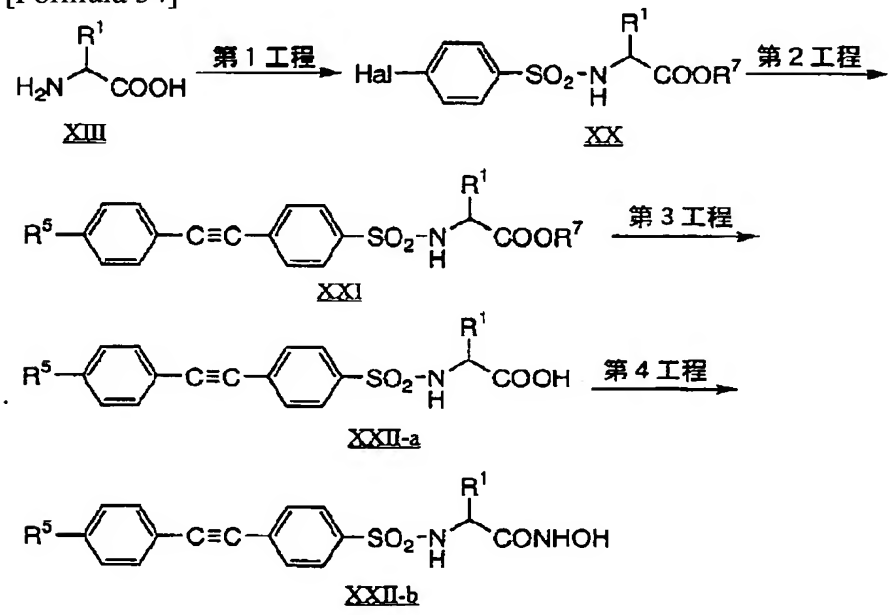
[0028] The reaction from a compound (XIII) to a compound (XV) is a reaction (the 1st process) which sulfonyl-izes the amino group of a compound (XIII), and can be performed like the A method 1st process. The reaction from a compound (XV) to a compound (XVI) is a reaction (the 2nd process) which changes an ethenyl substituent into an aldehyde. The reaction from a compound (XVI) to a compound (XVIII) is a reaction (the 3rd and 4th process) which makes a tetrazole ring build. The reaction from a compound (XVIII) to a compound (XIX-a) is a reaction (the 5th process) which performs N-alkylation of a compound (XVIII) etc. and clearance of a carboxy protective group, and can be performed like the A method 1st process. The reaction from a compound (XIX-a) to a compound (XIX-b) is a reaction (the 6th process) which changes a carboxylic-acid derivative into a hydroxamic acid derivative, and can be performed like the A method 2nd - the 4th process. It will be as follows if each process is described in more detail.

[0029] (The 1st process) It can carry out like the A method 1st process.

(The 2nd process) By adding ozone for a compound (XV) among solvents, such as dichloromethane, ethyl acetate, and a methanol, an ozonide is made to form, and by adding a zinc-acetic acid, triethyl phosphate, or a dimethyl sulfide into the succeedingly same system, reduction-processing can be performed and it can change into the target aldehyde derivative (compound (XVI)) (contact hydrogenation is sufficient as reduction-processing). reaction temperature -100 degrees C - a room temperature -- reaction time is 1 - 3 hours preferably under -78 degrees C - ice-cooling for 0.5 to 10 hours.

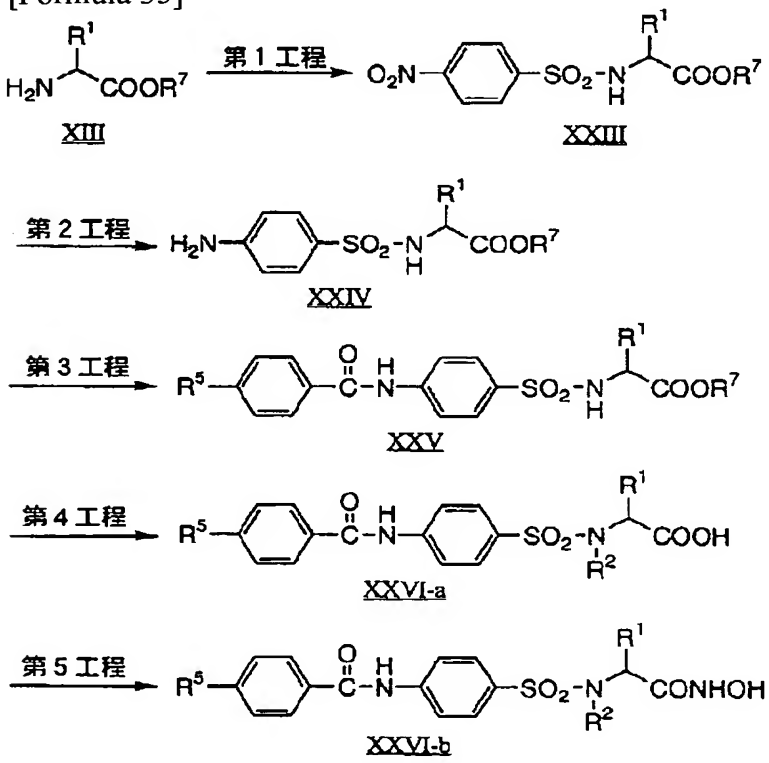
(The 3rd process) A compound (XVI) is convertible for the target compound (XVII)

by making benzenesulphonyl hydrazide react among the mixed solvent of solvents, such as a tetrahydrofuran and the ether, and solvents, such as a methanol and ethanol. reaction temperature -- bottom of ice-cooling - 80 degrees C of room temperature -50 degrees C and reaction time are 10 - 20 hours preferably for 3 to 30 hours.
(The 4th process) the aryl or the heteroaryl derivative which may be permuted which has amino groups, such as an aniline, and which may be permuted -- the mixed solvent of alcoholic (for example, ethanol etc.) - water -- dissolving -- the temperature in a system -20 degrees C - 10 degrees C -- desirable -- 0 degree C - 5 degrees C -- diazotation agents, such as concentrated hydrochloric acid and a sodium-nitrite water solution, -- in addition, it changes into diazonium salt. Reaction time is 10 - 30 minutes preferably for 5 minutes to 1 hour. It can be made to change into the target compound (XV) by adding this reaction solution to the pyridine solution of a compound (XVII), and making -30 degrees C - 50 degrees C react preferably at -15 degrees C - a room temperature for 2 to 5 hours for 1 to 10 hours. the case where it is a substituent with R1 and R5 acting as [substituent] the failure of this reaction -- Protective Groups in Organic Synthesis and Theodora W Green (John Wiley & Sons) etc. -- what is necessary is to protect beforehand by the approach of a publication and just to remove the protective group in a desirable phase
(The 5th process) It can carry out like the A method 1st process.
(The 6th process) It can carry out like the A method 2nd - the 4th process.
[0030] (The C method)
[Formula 34]



(The inside of a formula, and R1, R2, R7 and Hal are the above and this meaning)
[0031] The reaction from a compound (XIII) to a compound (XX) is a reaction (the 1st process) which sulfonyl-izes the amino group of a compound (XIII), and can be performed like the A method 1st process. The reaction from a compound (XX) to a compound (XXI) is a reaction (the 2nd process) which a guide peg makes the halogenation radical of phenyl a loan, and introduces a triple bond using the Heck (Heck) reaction (it indicates to K.Sonogashira, Y.Tohda, and N.Hagihara, Tetrahedron Lett., 4467 (1975), etc.). The reaction from a compound (XXI) to a compound (XXII-a) is a reaction (the 3rd process) which performs N-alkylation of a compound (XXI) etc. and clearance of a carboxy protective group, and can be

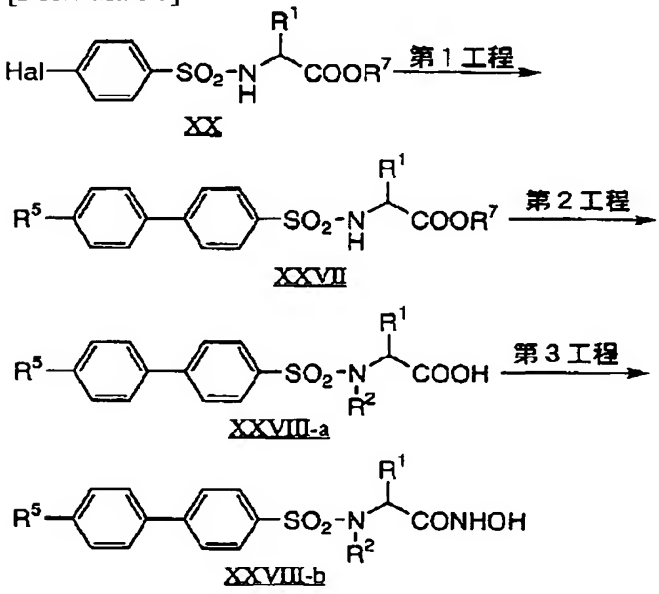
performed like the A method 1st process. The reaction from a compound (XXII-a) to a compound (XXII-b) is a reaction (the 4th process) which changes a carboxylic-acid derivative into a hydroxamic acid derivative, and can be performed like the A method 2nd - the 4th process. It will be as follows if each process is described in more detail.
(The 1st process) It can carry out like the A method 1st process.
A compound (XX) Dimethylformamide, toluene, a xylene, (The 2nd process) The inside of solvents, such as benzene and a tetrahydrofuran, a palladium catalyst (For example, Pd(Ph3P)2Cl2 grade), a univalent copper reagent Under existence of for example, (CuI etc. and organic bases) (for example, triethylamine, diisopropyl ethylamine, etc.), It is convertible for the compound (XXI) made into a (Heck reaction) and the object by making the derivative which has ethynyl groups, such as ethynyl benzene, (R5-phenyl-C(triple bond) C-) react. reaction temperature -- room temperature - 100 degrees C of room temperature -80 degrees C and reaction time are 10 - 20 hours preferably for 3 to 30 hours. the case where it is a substituent with R1 and R5 acting as [substituent] the failure of this reaction -- Protective Groups in Organic Synthesis and Theodora W Green (John Wiley& Sons) etc. -- what is necessary is to protect beforehand by the approach of a publication and just to remove the protective group in a desirable phase
(The 3rd process) It can carry out like the A method 1st process.
(The 4th process) It can carry out like the A method 2nd - the 4th process.
[0032] (The D method)
[Formula 35]



XIII　XXIII　XXIV　XXV　XXVI-a　XXVI-b

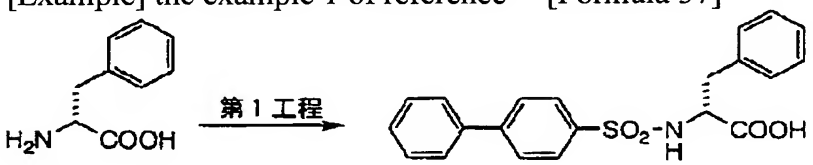
(The inside of a formula, and R1, R2 and R7 are the above and this meaning)
[0033] The reaction from a compound (XIII) to a compound (XXIII) is a reaction (the 1st process) which sulfonyl-izes the amino group of a compound (X), and can be performed like the A method 1st process. The reaction from a compound (XXIII) to a compound (XXIV) is a reaction (the 2nd process) which returns the nitration radical of phenyl to the amino group. It can carry out by the reaction condition of a catalytic

reduction method, hydrochloric-acid-iron, and hydrochloric-acid-tin etc. The reaction from a compound (XXIV) to a compound (XXV) is a reaction (the 3rd process) in which a guide peg makes the amino group of phenyl a loan, and amide association is made to form. Usually, the amide bonding reaction used can perform. The reaction from a compound (XXV) to a compound (XXVI-a) is a reaction (the 4th process) which performs N-alkylation of a compound (XXV) etc. and clearance of a carboxy protective group, and can be performed like the A method 1st process. The reaction from a compound (XXVI-a) to a compound (XXVI-b) is a reaction (the 5th process) which changes a carboxylic-acid derivative into a hydroxamic acid derivative, and can be performed like the A method 2nd - the 4th process. It will be as follows if each process is described in more detail.
(The 1st process) It can carry out like the A method 1st process.
(The 2nd process) The target compound (XXIV) can be obtained by making a compound (XXIII) react under ordinary pressure or application-of-pressure conditions among solvents, such as a methanol, ethanol, ethyl acetate, and an acetic acid, under existence of catalysts (Pd-C, PtO2, Raney nickel, etc.) and a hydrogen ambient atmosphere. reaction temperature -- bottom of ice-cooling - 80 degrees C of room temperature -50 degrees C and reaction time are 2 - 5 hours preferably for 1 to 10 hours.
A compound (XXIV) Dimethylformamide, a tetrahydrofuran, (The 3rd process) Dioxane, dimethyl sulfoxide, an acetonitrile, a xylene, toluene, the inside of solvents, such as benzene and dichloromethane, and a base (for example, triethylamine --) By making the aryl or the heteroaryl derivative which may be permuted which has acid halide functional groups (it is otherwise activity ester etc.), such as benzoyl chloride, under existence of N-methyl morpholine, potassium carbonate, etc. and which may be permuted react It is convertible for the target compound (XXV). reaction temperature -- bottom of ice-cooling - 100 degrees C of room temperature -60 degrees C and reaction time are 10 - 25 hours preferably for 3 to 30 hours.
(The 4th process) It can carry out like the A method 1st process.
(The 5th process) It can carry out like the A method 2nd - the 4th process.
[0034] (E law)
[Formula 36]



(The inside of a formula, and R1, R2, R5, R7 and Hal are the above and this meaning.)
[0035] the reaction from a compound (XX) to a compound (XXVII) -- the halogenation radical of phenyl -- a guide peg -- a loan -- carrying out -- the Suzuki reaction (M. it indicates to J.Sharp and V.Snieckus, Tetrahedron Lett.26, 5997 (1985), etc.) -- using (R5-phenyl) -- it is the reaction (the 1st process) to introduce. The reaction from a compound (XXVII) to a compound (XXVIII-a) is a reaction (the 2nd process) which performs N-alkylation of a compound (XXVII) etc. and clearance of a carboxy protective group, and can be performed like the A method 1st process. The reaction from a compound (XXVIII-a) to a compound (XXVIII-b) is a reaction (the 3rd process) which changes a carboxylic-acid derivative into a hydroxamic acid derivative, and can be performed like the A method 2nd - the 4th process. It will be as follows if each process is described in more detail.
A compound (XX) Dimethylformamide, toluene, a xylene, (The 1st process) The inside of solvents, such as benzene and a tetrahydrofuran, a palladium catalyst (for example, Pd(Ph3P) 4 grade) and a base (for example, potassium carbonate --) Under existence of a calcium carbonate, triethylamine, sodium methoxide, etc., It is convertible for the compound (XXVII) made into the (Suzuki reaction) and the object by making it react with the derivative which has B(OH)2 (it is otherwise B(Et)2 grade) radicals, such as a phenyl boron acid, (R5-phenyl). reaction temperature -- room temperature - 100 degrees C of room temperature -80 degrees C and reaction time are 15 - 30 hours preferably for 5 to 50 hours. the case where it is a substituent with R1 and R5 acting as [substituent] the failure of this reaction -- Protective Groups in Organic Synthesis and Theodora W Green (John Wiley & Sons) etc. -- what is necessary is to protect beforehand by the approach of a publication and just to remove the protective group in a desirable phase
(The 2nd process) It can carry out like the A method 1st process.
(The 3rd process) It can carry out like the A method 2nd - the 4th process.
[0036] When calling it the "this invention compound", conjugation also of the salt permitted on medicine manufacture or its hydrate is carried out. For example, a salt with alkali metal (a lithium, sodium, potassium, etc.), alkaline earth metal (magnesium, calcium, etc.), ammonium, an organic base and a salt with amino acid or inorganic acids (a hydrochloric acid, a hydrobromic acid, a phosphoric acid, sulfuric acid, etc.), and organic acids (an acetic acid, a citric acid, a maleic acid, a fumaric acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) is mentioned. These salts can be made to form by the approach usually performed. When forming a hydrate, you may configurate with the water molecule of the number of arbitration. Moreover, this invention compound is not limited to a specific isomer, and contains all possible isomers and racemic modification. As the publication of the example of an experiment mentioned later, this invention compound shows the outstanding MMP-8 inhibition activity, and checks matrix decomposition. Specifically The osteoarthritis, articular rheumatism, a corneal ulcer, periodontitis, a viral infectious disease Progress of (a HIV infectious disease [for example,]), the arteriosclerosis obliterans, the arteriosclerotic aneurysm, The atherosclerosis, restenosis, septicemia, septic shock, coronary thrombosis, and abnormality vascularization, The scleritis, multiple sclerosis, open-angle glaucoma, a retinopathy, a fecundity retinopathy, the neovascular glaucoma, The pterygium, keratitis, the bubble nature epidermolysis, psoriasis, diabetes mellitus, a nephritis, a nervous disease, It can be used as inflammation, osteoporosis, osteoclasis, gingivitis, tumor growth, a tumor vessel rebirth, an eye neoplasm, the hemangiofibroma, hemanglioma, fever, bleeding,

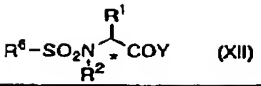
coagulation, cachexia, anorexia, a sudden sexually transmitted disease, a shock, autoimmune disease, malaria, Crohn's disease, meningitis, and a therapy agent of a gastroenteric ulcer. When medicating Homo sapiens with this invention compound for the purpose of the therapy of the above-mentioned disease, a medicine can be parenterally prescribed for the patient as an oral target or injections, suppositories, a percutaneous absorption agent, inhalations, etc. as powder, a granule, a tablet, a capsule, a pill, liquids and solutions, etc. Moreover, it can mix if needed and additives for remedies, such as the excipient and binder which fitted the effective dose of this compound at the pharmaceutical form, a wetting agent, disintegrator, and lubricant, can be considered as remedy pharmaceutical preparation. With support suitable in the case of injections, sterilization processing is performed and it considers as pharmaceutical preparation. Although a dose changes also with the condition of a disease, the administration root, a patient's age, or weights, when medicating an adult by taking orally, they are usually 0.1 - 100 mg/kg / day, and are 1 - 20 mg/kg / day preferably. This invention is not limited by these, although an example and the example of a trial are given to below and this invention is explained to it in more detail. The following codes are used among an example.
Me: Methyl tBu:tert-butyl DMSO:dimethyl-sulfoxide p-TsOH: P-toluenesulfonic acid
[0037]
[Example] the example 1 of reference -- [Formula 37]



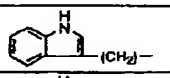
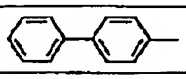
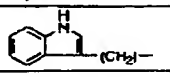
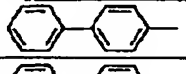
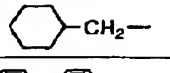
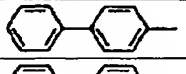
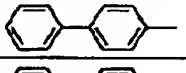
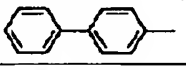
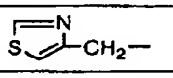
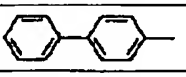
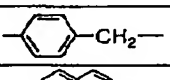
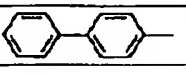
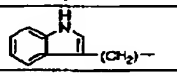
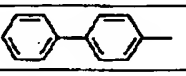
XX-1 1

[0038] 1st (process R)-(+)-phenylalanine (compound XX-1) Ice-cooling was added to dimethylformamide 50ml and 35ml suspension of water of 1.65 g (10mmol), and triethylamine 2.78ml (20mmol) was added to the bottom of churning. Subsequently, the 4-biphenyl sulfonyl chloride 2.52g (10mmol) dimethylformamide 10ml solution was added in 5 minutes. 1-hydroxy benzotriazol hydrate 1.35g (10mmol), 2.1g [of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochlorides] (11mmol), 3.47g [of hydroxylamine hydrochlorides] (50mmol), and triethylamine 7ml (50mmol) was added after 2-hour churning at this temperature. After 16-hour churning and reaction mixture were poured into water at the room temperature, and ethyl acetate extracted. Sequential washing was carried out with 2N-hydrochloric acid, 5% sodium-hydrogencarbonate water solution, and water. If the parts which give residue to a silica gel column chromatography after vacuum concentration, and are eluted in chloroform / methanol =40/1 to 20/1 are collected, it is bubble-like residue (compound (1)). 1.70 g was obtained. 43% of yield.
The 169 to 170 degree C melting point.
elemental-analysis value (%) C21H20N2O4S calculated-value: -- C; 63.62, H; 5.08, N; 7.07, S;8.09 experimental-value:C;63.61, H; 5.12, N; 6.98, and S;8.06IRnumax(cm-1) (Nujol):3365 -- 3295, 3266, 1674, 1320, and 1159NMR(deltappm) d6-DMSO:2.61 (dd, J= 8.6, 13.4 Hz, 1H), 2.80 (dd, J= 6.0, 13.6 Hz, 1H) and 3.80 [(m, 1H) alpha] D : The same reaction as +18.5 **1.2 (c= 0.503%, 25 degree C, DMSO) example 1, Above A -- law -E -- the compound (2) - the compound (50) were compounded according to law and an approach given in WO 97/27174. The physical data was shown in the following tables 1-12.

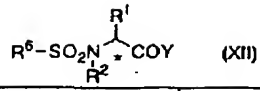
[0039]
[A table 1]



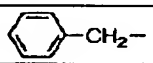
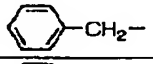
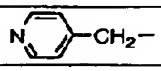
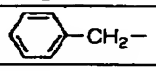
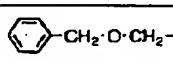
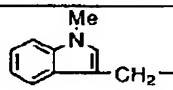
(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
2		H		OH	R	2.88(dd, J=8.0, 14.0 Hz, 1H), 3.09(dd, J=6.0, 14.0 Hz, 1H), 3.91(m, 1H), 8.23(m, 1H), 10.79(s 1H), 12.70(br, 1H)
3		H		NHOH	R	2.72(dd, J=7.2, 13.8 Hz, 1H), 2.97(dd, J=7.0, 14.8 Hz, 1H), 3.81(m, 1H)
4	CF_3CH_2-	H		NHOH	R	2.2-2.7(m, 2H), 3.99(t, J=7.0 Hz, 1H)
5		H		NHOH	R	0.50-1.62(m, 13H), 3.56(t, J=7.4 Hz, 1H)
6		H		NHOH	R	2.67(dd, J=9.2, 13.1 Hz, 1H), 2.84(dd, J=5.3, 13.5 Hz, 1H), 3.82(m, 1H)
7	HO_2HC-	H		NHOH	R	3.29(dd, J=6.7, 10.7 Hz, 1H), 3.43(dd, J=8.4, 10.7 Hz, 1H), 3.62(m, 1H), 7.85(q, J=8.7 Hz, 2H), 7.88(q, J=8.7 Hz, 2H), 7.98(d, J=7.8 Hz, 1H), 10.61(s, 1H)
8		H		NHOH	RS	2.87(dd, J=5.6, 14.2 Hz, 1H), 2.98(dd, J=8.4, 14.2 Hz, 1H), 4.02(dd, J=2.2, 8.6 Hz, 1H), 7.24(d, J=2.0 Hz, 1H), 8.83(d, J=2.2 Hz, 1H)
9		H		NHOH	RS	2.62(dd, J=9.9, 13.5 Hz, 1H), 2.78(dd, J=5.8, 13.0 Hz, 1H), 3.77(t, J=6.2 HZ, 1H)
10		H		NHOH	RS	3.12(dd, J=10.3, 14.3 Hz, 1H), 3.89(dd, J=3.3, 13.5 Hz, 1H), 4.20(m, 2H), 5.90(brs, 1H)
11		CH_3		NHOH	R	2.83(m, 1H), 3.03(s, 3H), 3.43(m, 1H), 4.76(m, 1H) (CDCl₃)

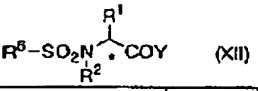
[0040]
[A table 2]



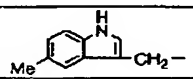
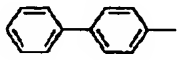
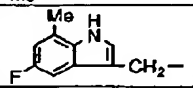
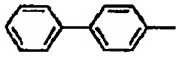
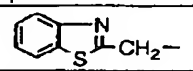
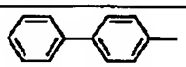
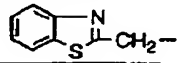
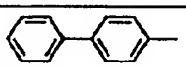
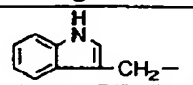
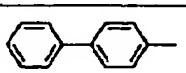
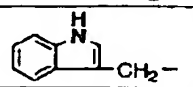
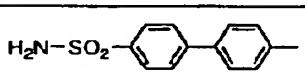
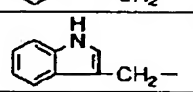
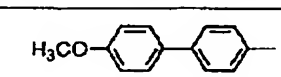
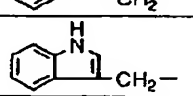
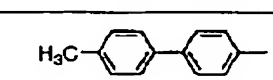
(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
12	$(CH_3)_2CH$-	H		OH	R	0.81(d, J=6.9 Hz, 3H), 0.84(d, J=6.6 Hz, 3H), 1.32(s, 9H)
13	$(CH_3)_2CH$-	H		OH	R	0.82(d, J=6.6 Hz, 3H), 0.85(d, J=6.2 Hz, 3H), 1.94(m, 1H), 3.58(m, 1H)
14	$(CH_3)_2CH$-	H		OH	R	0.82(d, J=6.2 Hz, 3H), 0.85(d, J=6.2 Hz, 3H), 1.96(m, 1H), 3.57(m, 1H)
15	$HOOCCH_2CH_2$-	H		OH	R	1.68(dd, J=7.9, 14.1 Hz, 1H), 1.87(dd, J=6.0, 14.1 Hz, 1H), 2.22(t, J=7.2 Hz, 2H), 3.80(m, 1H)
16		H		NHOH	R	2.61(dd, J=8.6, 13.4 Hz, 1H), 2.80(dd, J=6.0, 13.6 Hz, 1H), 3.80(m, 1H)
17		H		NHOH	RS	1.68(m, 2H), 2.37(m, 2H), 3.64(t, J=6.9 Hz, 1H)
18		H		NHOH	RS	2.68(dd, J=9.8, 13.7 Hz, 1H), 2.79(dd, J=5.6, 12.8 Hz, 1H), 3.85(t, J=7.0 Hz, 1H)
19		H		NHOH	R	4.88(d, J=9.4 Hz, 1H), 8.74(d, J=9.4 Hz, 1H), 8.98(s, 1H), 10.92(s, 1H)
20		H		NHOH	R	2.69(dd, J=7.6, 13.5 Hz, 1H), 2.93(dd, J=7.6, 13.5 Hz, 1H), 3.77(t, J=7.6 Hz, 1H) (CD_3OD)
21		H		NHOH	RS	2.71(dd, J=7.9, 14.2 Hz, 1H), 2.94(dd, J=6.9, 14.2 Hz, 1H), 3.57(s, 3H), 3.83(dd, J=7.0, 7.4 Hz, 1H)

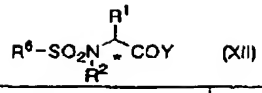
[0041]
[0042]
[A table 3]



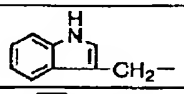
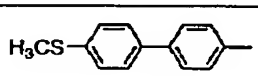
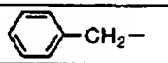
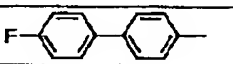
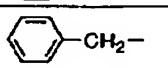
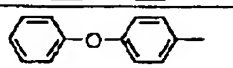
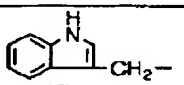
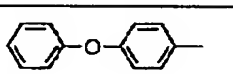
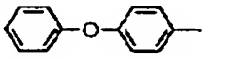
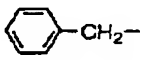
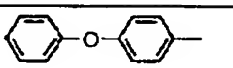
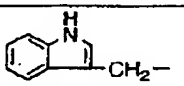
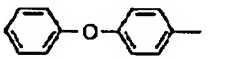
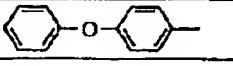
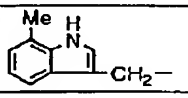
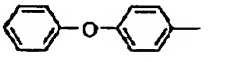
(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
22		H		NHOH	RS	2.25(s, 3H), 2.67(dd, J=7.5, 14.2 Hz, 1H), 2.95(dd, J=7.7, 14.2 Hz, 1H), 3.81(dd, J=6.2, 14.2 Hz, 1H)
23		H		NHOH	RS	2.72(dd, J=8.0, 14.0 Hz, 1H), 2.90(dd, J=6.2, 14.2 Hz, 1H), 3.82(m, 1H)
24		H		OH	RS	3.24-3.56(m, 2H), 4.34(m, 1H)
25		H		NHOH	RS	3.22-3.38(m, 2H), 4.17-4.24(m, 2H), 7.80(d, J=8.0 Hz, 2H), 7.96(d, J=6.4 Hz, 2H)
26		Bn		NHOH	R	2.88(m, 1H), 3.42(m, 1H), 4.51(br.s, 1H), 4.66(d, J=15.6 Hz, 1H), 4.78(d, J=15.6 Hz, 1H)
27		H		OH	R	–
28		H		OH	R	2.89(dd, J=7.5, 14.4 Hz, 1H), 3.08(dd, J=6.0, 14.4 Hz, 1H), 3.81(s, 3H)
29		H		OH	R	2.36(s, 1H), 2.86(dd, J=8.0, 14.8 Hz, 1H),, 3.11(dd, J=5.8, 14.8 Hz, 1H)

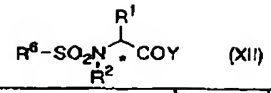
[0043]
[A table 4]



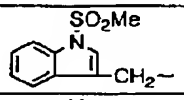
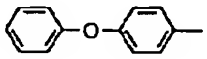
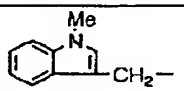
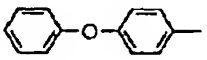
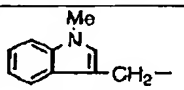
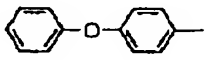
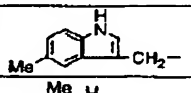
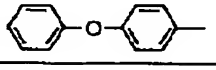
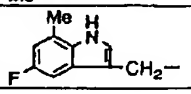
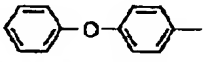
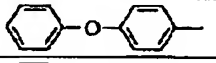
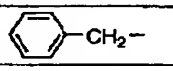
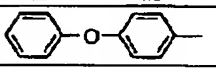
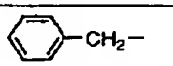
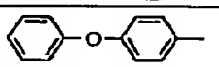
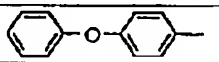
(XII)

実施例 No.	R^1	R^2	R^6	Y	*	^{1}H-NMR(δ ppm) d_6-DMSO
30		H		OH	R	2.53(s, 3H), 2.86(dd, J=8.2, 14.0 Hz, 1H), 3.08(dd, J=6.0, 14.0 Hz, 1H)
31		H		OH	R	2.73(dd, J=9.8, 14.6 Hz, 1H), 2.97(dd, J=5.6, 14.6 Hz, 1H), 3.89(m, 1H)
32		H		OH	R	2.72(dd, J=8.7, 13.6Hz, 1H), 2.94(dd, J=5.6, 13.6 Hz, 1H), 3.84(ddd, J=5.6, 8.7, 8.7 Hz, 1H), 8.23(d, J=8.7Hz)
33		H		OH	R	2.88(dd, J=7.4, 15.2 Hz, 1H), 3.07(dd, J=6.2, 14.4 Hz, 1H), 3.83(m, 1H), 8.08(m, 1H), 10.80(s, 1H), 12.70(br, 1H)
34	$(CH_3)_2CH$-	H		OH	R	0.89(d, J=7.0 Hz, 3H), 0.98(d, J=6.8 Hz, 3H), 2.12(m, 2H), 3.80(dd, J=4.7, 9.7 Hz, 1H), 5.17(d, J=9.6Hz, 1H)
35		H		NHOH	R	2.72(dd, J=8.7, 13.6 Hz, 1H), 2.94(dd, J=5.6, 13.6 Hz, 1H), 3.84(ddd, J=5.6, 8.7, 8.7 Hz, 1H), 8.23(d, J=8.7 Hz, 1H)
36		H		NHOH	R	2.71(dd, J=7.0, 14.4 Hz, 1H), 2.96(dd, J=7.0, 14.2 Hz, 1H), 3.78(t, J=7.6 Hz, 1H)
37	$(CH_3)_2CH$-	H		NHOH	R	0.76(d, J=6.6 Hz, 6H), 1.77(m, 1H), 3.26(m, 1H)
38		H		OH	RS	2.46(s, 3H), 2.89(dd, J=8.0, 14.0 Hz, 1H), 3.08(dd, J=6.8, 14.0 Hz, 1H)

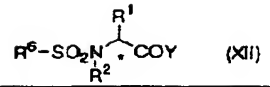
[0044]
[A table 5]



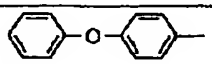
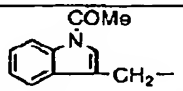
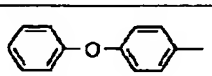
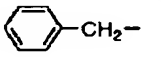
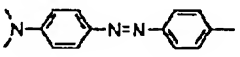
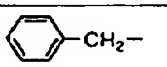
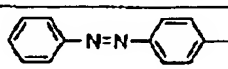
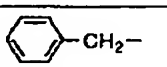
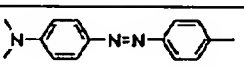
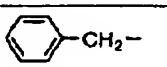
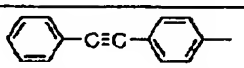
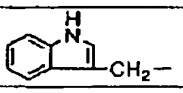
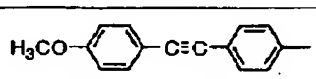
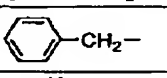
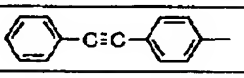
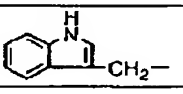
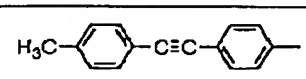
(XII)

実施例 No.	R^1	R^2	R^6	Y	*	^{1}H-NMR(δ ppm) d_6-DMSO
39		H		OH	RS	2.90(dd, J=9.0, 14.5 Hz, 1H), 3.09(dd, J=5.2, 14.5 Hz, 1H), 3.28(s, 3H)
40		H		OH	RS	3.18(dd, J=6.5, 14.9 Hz, 1H), 3.28(dd, J=6.3, 14.9 Hz, 1H), 3.69(s, 3H)
41		H		NHOH	RS	2.71(dd, J=7.9, 14.2 Hz, 1H), 2.93(dd, J=6.5, 14.3 Hz, 1H), 3.65(s, 3H), 3.78(dd, J=7.1, 7.2 Hz, 1H)
42		H		NHOH	RS	2.34(s, 3H), 2.65(dd, J=7.8, 14.1 Hz, 1H), 2.93(dd, J=7.6, 14.4 Hz, 1H), 3.75(dd, J=6.8, 7.7 Hz, 1H)
43		H		NHOH	RS	2.71(dd, J=8.9, 14.4 Hz, 1H), 2.89(dd, J=6.6, 14.4 Hz, 1H), 3.75(dd, J=6.5, 6.8 Hz, 1H)
44	$(CH_3)_2CH$-	Bn		OH	R	0.80(d, J=6.8 Hz, 1H), 0.91(d, J=6.2 Hz, 3H), 2.03(m, 1H), 4.19(d, J=10.6 Hz, 1H) ($CDCl_3$)
45		CH_3		NHOH	R	2.72(dd, J=8.4, 13.8 Hz, 1H), 2.89(s, 3H), 3.31(dd, J=7.2, 13.8 Hz, 1H) ($CDCl_3$)
46		Bn		NHOH	R	2.69(dd, J=6.1, 13.6 Hz, 1H), 3.27(dd, J=9.1, 13.6 Hz, 1H), 4.61(ABq, J=15.5 Hz, 2H) ($CDCl_3$)
47	$(CH_3)_2CH$-	CH_3		NHOH	R	0.71(d, J=6.6 Hz, 3H), 0.88(d, J=6.4 Hz, 3H), 2.88(s, 3H), 3.48(d, J=10.8 Hz, 1H)

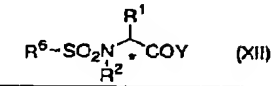
[0045]
[A table 6]



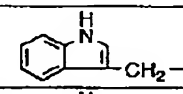
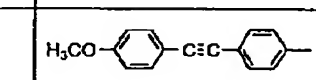
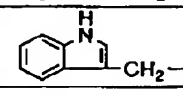
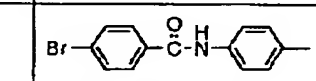
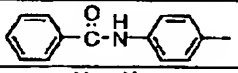
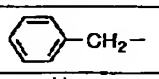
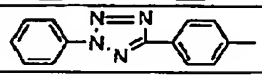
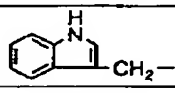
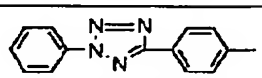
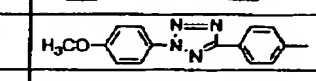
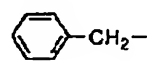
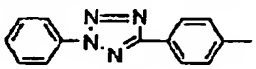
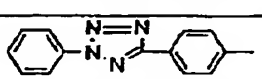
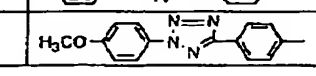
(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
48	$(CH_3)_2CH$-	Bn		NHOH	R	0.55(d, J=6.8 Hz, 3H), 0.82(d, J=6.6 Hz, 3H), 3.74(s, 3H)
49		H		NHOH	RS	2.54(s, 3H), 2.69-2.89(m, 2H), 3.87(m, 1H)
50		H		OH	R	2.62(dd, J=8.6, 13.5 Hz, 1H), 2.81(dd, J=6.5, 13.6 Hz, 1H), 3.09(s, 6H), 3.83(m, 1H), 6.86(d, J=9.0 Hz, 2H), 7.83(d, J=8.8 Hz, 2H)
51		H		NHOH	R	2.65(dd, J=8.9, 13.6 Hz, 1H), 2.82(dd, J=6.6, 13.6 Hz, 1H), 3.86(m, 1H), 7.75(d, J=7.8 Hz, 2H), 7.87(d, J=8.7Hz, 2H)
52		H		NHOH	R	2.62(dd, J=8.6, 13.5 Hz, 1H), 2.81(dd, J=6.5, 13.6 Hz, 1H), 3.09(s, 6H), 3.83(m, 1H), 6.86(d, J=9.0 Hz, 2H), 7.83(d, J=8.8 Hz, 2H)
53		H		OH	R	2.73(dd, J=9.3, 13.6 Hz, 1H), 2.96(dd, J=5.4, 13.5 Hz, 1H), 3.92(dt, J=5.4, 9.3 Hz, 1H), 8.42(d, J=9.3 Hz, 1H)
54		H		OH	R	2.87(dd, J=7.8, 14.2 Hz, 1H), 3.08(dd, J=6.2, 14.2 Hz, 1H), 3.81(s, 3H)
55		H		NHOH	R	2.62(dd, J=8.4, 13.5 Hz, 1H), 2.80(dd, J=6.0, 13.5 Hz, 1H), 3.82(ddd, J=6.0, 8.4, 8.7 Hz, 1H), 8.38(d, J=8.7 Hz, 1H)
56		H		NHOH	R	2.36(s, 3H), 2.73(dd, J=8.1, 14.1 Hz, 1H), 2.96(dd, J=6.6, 14.1 Hz, 1H), 3.84(dd, J=8.1, 15.3 Hz, 1H),

[0046]
[A table 7]



(XII)

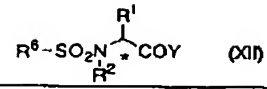
実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
57		H		NHOH	R	2.73(dd, J=8.1, 14.1 Hz, 1H), 2.95(dd, J=6.9, 14.1 Hz, 1H), 3.81(s, 3H)
58		H		OH	R	2.87(dd, J=7.8, 14.6 Hz, 1H), 3.07(dd, J=6.6, 14.6 Hz, 1H), 3.93(m, 1H)
59	$(CH_3)_2CH$-	H		NHOH	R	0.75(d, J=6.9 Hz, 3H), 0.77(d, J=6.9 Hz, 3H), 1.78(m, 1H), 3.30(m, 1H)
60		H		OH	R	2.75(dd, J=9.3, 13.7 Hz, 1H), 2.99(dd, J=5.3, 13.7 Hz, 1H), 3.96(dt, J=5.3, 9.3 Hz, 1H), 8.53(d, J=9.3 Hz, 1H)
61		H		OH	R	3.03(dd, J=6.5, 15.1 Hz, 1H), 3.15(dd, J=4.7, 15.1 Hz, 1H), 3.64(t, J=5.1 Hz, 1H)
62	$(CH_3)_2CH$-	H		OH	R	0.81(d, J=6.9 Hz, 3H), 0.85(d, J=6.9Hz, 3H), 1.97(m, 1H), 3.59(m, 1H), 3.88(s, 3H)
63		H		NHOH	R	2.65(dd, J=9.3, 13.1 Hz, 1H), 2.82(dd, J=5.8, 13.1 Hz, 1H), 3.86(dt, J=5.8, 9.3 Hz, Hz, 1H), 7.72(q, J=8.1 Hz, 1H), 8.19(q, J=8.1 Hz, 2H), 8.49(d, J=9.3 Hz, 1H), 8.88(s, 1H), 10.69(s, 1H)
64	$(CH_3)_2CH$-	H		NHOH	R	0.78(d, J=6.8 Hz, 6H), 1.80(m, 1H)
65	$(CH_3)_2CH$-	H		NHOH	R	0.78(d, J=6.9 Hz, 6H), 1.79(m, 1H), 3.36(s, 3H)

[0047]
[A table 8]

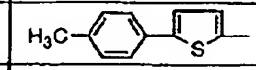
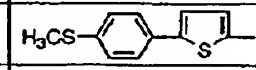
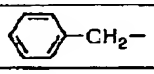
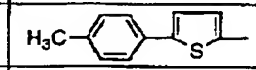
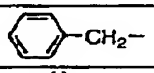
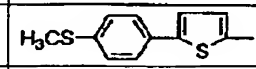
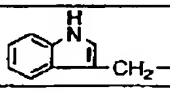
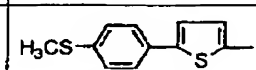
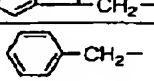
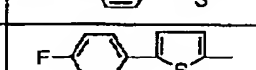
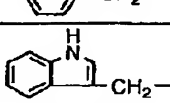
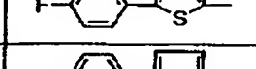
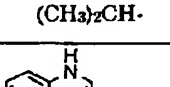
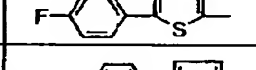
(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
66		H		OH	R	2.54(s, 3H), 2.81(dd, J=8.2, 14.6 Hz, 1H), 3.12(dd, J=6.0, 14.6 Hz, 1H), 4.02(m, 1H)
67		H		OH	R	2.92(dd, J=8.6, 14.8 Hz, 1H), 3.13(dd, J=5.8, 14.4 Hz, 1H), 3.98(dd, J=5.6, 8.2 Hz, 1H)
68		H		OH	R	3.20(m, 2H), 3.68(m, 1H), 3.81(s, 3H)
69		H		NHOH	R	2.36(s, 3H), 2.80(m, 1H), 3.00(m, 1H), 3.92(br.s, 1H)
70		H		NHOH	R	2.81(dd, J=8.4, 14.4 Hz, 1H), 3.00(dd, J=6.3, 14.4 Hz, 1H), 3.91(m, 1H)
71	$(CH_3)_2CH$-	H		OH	R	0.79(d, J=6.9 Hz, 3H), 0.88(d, J=6.9 Hz, 3H), 2.07(s, 3H), 2.60(m, 1H)
72	$(CH_3)_2CH$-	H		OH	R	1.11(d, J=6.8 Hz, 3H), 1.17(d, J=6.8 Hz, 1H), 2.81(s, 3H)
73	$(CH_3)_2CH$-	H		NHOH	R	0.80(d, J=6.0 Hz, 6H), 1.82(m, 1H), 2.35(s, 3H)
74	$(CH_3)_2CH$-	H		NHOH	R	0.79(d, J=6.6 Hz, 3H), 1.82(m, 1H), 3.32(s, 3H), 3.36(m, 1H)

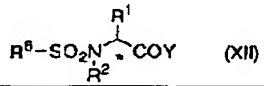
[0048]
[A table 9]



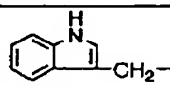
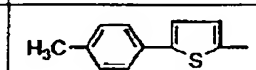
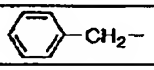
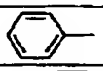
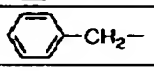
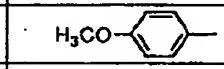
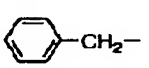
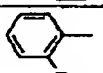
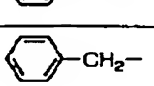
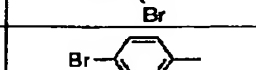
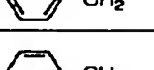
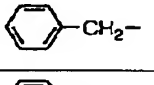
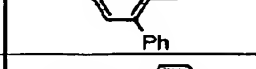
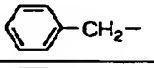
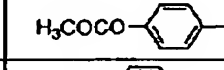
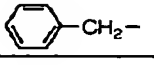
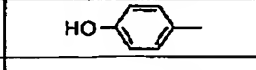
(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
75	$(CH_3)_2CH$-	H		OH	R	0.82(d, J=6.6 Hz, 3H), 0.87(d, J=6.6 Hz, 3H), 2.00(m, 1H), 3.61(dd, J=5.9, 9.3 Hz, 1H)
76	$(CH_3)_2CH$-	H		OH	R	0.82(d, J=7.0 Hz, 3H), 0.87(d, J=7.0 Hz, 3H), 1.98(m, 1H), 2.51(s, 3H)
77		H		OH	R	2.35(s, 3H), 2.75(dd, J=9.6, 13.2 Hz, 1H), 2.99(dd, J=5.6, 13.6 Hz, 1H)
78		H		OH	R	2.52(s, 3H), 2.75(dd, J=9.5, 13.7 Hz, 1H), 2.99(dd, J=5.3, 13.7 Hz, 1H)
79		H		OH	R	2.53(s, 3H), 2.92(dd, J=7.8, 14.4 Hz, 1H), 3.11(dd, J=6.2, 14.4 Hz, 1H)
80		H		OH	R	2.75(dd, J=9.6, 14.0 Hz, 1H), 3.02(dd, J=4.8, 14.0 Hz, 1H), 3.98(m, 1H)
81		H		OH	R	2.92(dd, J=8.4, 14.2 Hz, 1H), 3.12(dd, J=5.8, 14.2 Hz, 1H), 4.00(m, 1H)
82	$(CH_3)_2CH$-	H		OH	R	0.83(d, J=6.6 Hz, 3H), 0.87(d, J=6.9 Hz, 3H), 3.61(dd, J=6.0, 9.3 Hz, 1H)
83		H		OH	R	2.91(dd, J=7.6, 14.6 Hz, 1H), 3.11(dd, J=6.4, 14.6 Hz, 1H), 3.81(s, 3H)

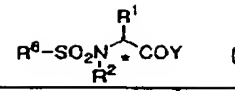
[0049]
[A table 10]



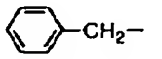
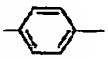
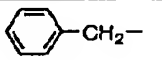
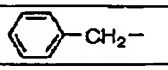
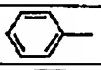
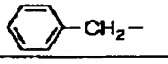
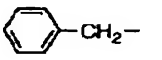
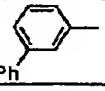
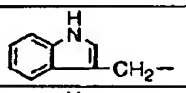
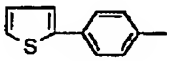
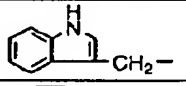
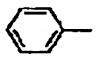
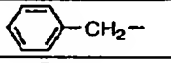
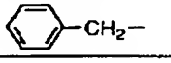
(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
84		H		OH	R	2.34(s, 3H), 2.91(dd, J=8.4, 14.2 Hz, 1H), 3.11(dd, J=6.4, 14.2 Hz, 1H)
85		H		NHOH	R	2.55(dd, J=6.6, 13.6, 1H), 2.79(dd, J=6.6, 13.6 Hz, 1H), 3.78(dt, J=6.4, 8.0 Hz, 1H)
86		H		NHOH	R	2.55(dd, J=8.0, 13.6, 1H), 2.77(dd, J=6.8, 13.6 Hz, 1H), 3.81(s, 3H)
87		H		NHOH	R	2.90-3.10(m, 2H), 4.10(m, 1H), 5.76(m, 1H)
88		H		NHOH	R	2.61(dd, J=9.4, 13.8 Hz, 1H), 2.78(dd, J=6.0, 13.8 Hz, 1H), 3.78(m, 1H), 7.43(d, J=8.2 Hz, 2H), 7.60(d, J=8.2 Hz, 2H)
89		H		NHOH	R	2.74-2.90(m, 2H), 3.88(m, 1H), 4.66(m, 1H)
90		H		NHOH	R	2.30(s, 3H), 2.71(dd, J=7.8, 13.6 Hz, 1H), 2.96(dd, J=7.4, 13.6 Hz, 1H), 3.82(dd, J=7.4, 8.8 Hz, 1H) (CD_3OD)
91		H		NHOH	R	2.69(dd, J=7.6, 13.5 Hz, 1H), 2.93(dd, J=7.6, 13.5 Hz, 1H), 3.77(t, J=7.6 Hz, 1H) (CD_3OD)
92		H		NHOH	R	0.90(t, J=6.8 Hz, 3H), 1.22-1.40(m, 4H), 1.52-1.67(m, 2H), 2.62(t, J=7.7Hz, 2H), 2.86(dd, J=8.4, 13.7 Hz, 1H), 3.02(dd, J=5.7, 13.7 Hz, 1H) ($CDCl_3$)

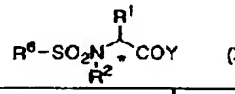
[0050]
[A table 11]



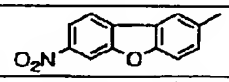
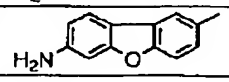
(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
93		H		NHOH	R	0.71(d, J=6.8 Hz, 3H), 0.74(d, J=6.4 Hz, 3H), 1.73(m, 1H), 3.22(m, 1H), 3.82(s, 3H), 7.05(d, J=9.0 Hz, 2H), 7.69(d, J=9.0 Hz, 2H)
94		Bn		NHOH	R	2.63(dd, J=6.8, 13.6 Hz, 1H), 3.23(dd, J=9.0, 13.6 Hz, 1H), 4.54(d, J=15.6 Hz, 1H), 4.68(d, J=15.6 Hz, 1H)
95		Bn		NHOH	S	2.53(m, 1H), 3.01(m, 1H), 4.49-4.58(m, 2H)
96		H		NHOH	R	2.60(dd, J=9.0, 13.8 Hz, 1H), 2.79(dd, J=9.3, 13.8 Hz, 1H), 3.76(m, 1H)
97		H		NHOH	R	2.84-3.10(m, 2H), 4.02(m, 1H), 3.35(m, 1H)
98		H		OH	R	2.87(dd, J=8.0, 14.6 Hz, 1H), 3.08(dd, J=6.5, 14.6 Hz, 1H), 4.00(m, 1H)
99		Bn		NHOH	R	0.87(t, J=6.3 Hz, 3H), 2.50(t, J=7.4 Hz, 2H), 2.76(dd, J=9.6, 14.0 Hz, 1H), 2.87(dd, J=5.8, 14.0 Hz, 1H), 3.84(dd, J=5.8, 9.6 Hz, 1H)
100		H	$CH_3(CH_2)_8CH_2$-	NHOH	R	2.80(dd, J=4.6, 14.0 Hz, 1H), 3.40(dd, J=9.4, 14.0 Hz, 1H), 4.46(m, 1H)
101		H		NHOH	R	2.79(dd, J=8.5, 13.4 Hz, 1H), 2.89(dd, J=6.4, 13.4 Hz, 1H), 6.55(d, J=15.5 Hz, 1H)

[0051]
[A table 12]



(XII)

実施例 No.	R¹	R²	R⁶	Y	*	¹H-NMR(δ ppm) d₆-DMSO
102	$(CH_3)_2CH$-	H		OH	R	0.80(d, J=6.6 Hz, 3H), 0.84(d, J=6.9 Hz, 3H), 1.97(m, 1H), 3.63(m, 1H)
103	$(CH_3)_2CH$-	H		OH	R	0.78(d, J=6.9 Hz, 3H), 0.82(d, J=6.9 Hz, 3H), 1.91(m, 1H), 3.14(m, 1H)

[0052] Example example 1 Catalytic domain (99Phe-262Gly) was amplified by PCR using isolation of MMP-8, and Human Bone Marrow cDNA of purification marketing. Cloning of this was carried out to Escherichia coli expression vector pTrc99A which introduced at least a His tag and the enterokinase cutting section, and the induction manifestation was performed and it was discovered to the insoluble fraction with IPTG (Isopropyl-beta-D-thiogalactopyranosi de). Walid Qoronfleh Thau F.Ho and M. -- Robert C.Wahl Trica A.Pulvino, Karen J.Vavra, Joe Falvo, Tracey M.Banks, Patricia G.Brake and Richard B.Ciccarelli:Gene expression, purification and characterization of recombinant human neutrophil collagenase. Gene 146 (1994), 297-301, and these data It changed a little and prepared. Isolation of MMP-8 was isolated from the insoluble fraction with the metal chelate chromatography, after

dissolving in a modifier (6M urea) with a conventional method. Subsequently, while dialysis removed the modifier (6M urea), RIFORUDINGU of an enzyme was performed, and active MMP-8 were obtained.
Example 2 The enzyme activity measuring method of enzyme inhibition activity measuring method MMP-8 of MMP-8 is C.Graham Knight and Frances Willenbrock andGillian Murphy. : A novel coumarin-labelled peptide for sensitive continuous assays of the matrix metallproteinases: It applied to the approach of FEBS LETT., 296, (1992), and 263-266 correspondingly. Substrate: MOCAc-Pro-Leu-Gly-Leu-A2Pr(DNP)-Ala-Arg-NH2 used Peptide Institute, Inc.Osaka, and Japan. The assay of an inhibitor performs the following four assays about one compound (inhibitor).
(A) Fluorescence intensity was measured about a substrate (synthetic substrate), an enzyme (MMP-8), an inhibitor (B) substrate (synthetic substrate), an inhibitor (C) substrate (synthetic substrate), and each enzyme (MMP-8) (D) substrate (synthetic substrate), and it asked for inhibition (%) by the degree type.
The rate of inhibition obtained inhibition (%) ={1-(A-B)/(C-D)} x100 was shown in a table 13.
[0053]
[A table 13]

化合物 No.	1000 nM 阻害 (%)	化合物 No.	1000 nM 阻害 (%)	化合物 No.	1000 nM 阻害 (%)
1	87.4	36	99.7	71	79.5
2	94.5	37	101.4	72	99.8
3	100.0	38	89.6	73	95.3
4	101.0	39	89.8	74	99.3
5	99.8	40	95.9	75	99.4
6	100.0	41	99.8	76	79.7
7	101.2	42	98.9	77	95.7
8	97.6	43	98.5	78	85.6
9	101.8	44	99.6	79	101.5
10	99.9	45	98.2	80	95.7
11	99.6	46	100.7	81	98.3
12	94.0	47	100.5	82	98.2
13	98.9	48	99.6	83	101.6
14	93.9	49	101.2	84	101.0
15	83.7	50	78.3	85	95.5
16	98.2	51	96.1	86	97.5
17	101.6	52	100.1	87	86.6
18	94.4	53	86.6	88	97.5
19	100.7	54	94.6	89	88.7
20	100.9	55	99.8	90	98.7
21	97.4	56	101.8	91	97.7
22	102.3	57	101.8	92	90.1
23	96.3	58	79.5	93	99.5
24	83.3	59	99.8	94	99.5
25	101.1	60	82.5	95	83.3
26	99.2	61	77.8	96	91.3
27	94.5	62	95.8	97	96.0
28	99.1	63	98.5	98	95.7
29	101.8	64	101.4	99	98.8
30	100.0	65	100.8	100	99.7
31	91.7	66	99.1	101	95.4
32	95.1	67	101.0	102	84.8
33	100.3	68	95.7	103	95.3
34	95.0	69	85.6		
35	100.9	70	101.5		

[0054] The granule containing an one or less example [of the example pharmaceutical preparation of pharmaceutical preparation] component is manufactured.
A component The compound expressed with a formula (I) 10 mg A lactose 700 mg Corn starch 274 mg HPC-L 16 mg It lets the compound and lactose which are expressed with 1000 mg types (I) pass to the screen of 60 meshes. It lets corn starch pass to the screen of 120 meshes. These are mixed in a V shaped rotary mixer. A HPC-L (hypoviscosity hydroxypropylcellulose) water solution is added after mixing, and it dries, after corning (0.5-1mm of extrusion granulation apertures), kneading and. The obtained desiccation granulation is ****(ed) with the vibrating screen (12/60 mesh), and a granule is obtained.
The powder for encapsulation containing a two or less example [of pharmaceutical preparation] component is manufactured.
A component The compound expressed with a formula (I) 10 mg A lactose 79 mg Corn starch 10 mg Magnesium stearate 1 mg It lets the compound and lactose which are expressed with 100 mg types (I) pass to the screen of 60 meshes. It lets corn starch pass to the screen of 120 meshes. These and magnesium stearate are mixed in a V shaped rotary mixer. A No. 5 ** gelatine capsule is filled up with 100mg of 10 trituration.
The granule for encapsulation containing a three or less example [of pharmaceutical preparation] component is manufactured.
A component The compound expressed with a formula (I) 15 mg A lactose 90 mg Corn starch 42 mg HPC-L 3 mg It lets the compound and lactose which are expressed with 150 mg types (I) pass to the screen of 60 meshes. It lets corn starch pass to the screen of 120 meshes. These are mixed, and it adds [after mixing] a HPC-L solution and dries [knead, corn and]. It is filled up with the obtained desiccation granulation after a particle size regulation, and a No. 4 ** gelatine capsule is filled up with the 150mg.
The tablet containing a four or less example [of pharmaceutical preparation] component is manufactured.
A component The compound expressed with a formula (I) 10 mg A lactose 90 mg A microcrystal cellulose 30 mg CMC-Na 15 mg magnesium stearate 5 mg It lets the compound expressed with 150 mg types (I), a lactose, a microcrystal cellulose, and CMC-Na (carboxymethylcellulose sodium salt) pass to the screen of 60 meshes, and mixes. Magnesium stearate mixing is carried out after mixing, and the end for tabletting of mixing is obtained. The end of this mixing is ****(ed) and a 150mg tablet is obtained.
[0055]
[Effect of the Invention] The sulfonamide derivative concerning this invention has MMP-8 inhibitory action, and found out that it might function effectively as therapy agents, such as rheumatoid arthritis and osteoarthritis.

[Translation done.]